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(60)	O) Parent Application or Grant UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY ROBERT WOOD JOHNSON MEDICAL SCHOOL [/]; (). YURCHENCO, Peter [/]; (). YURCHENCO, Peter [/]; (). HARPER, David, S.; ().				

- (54) Title: LAMININ 2 AND METHODS FOR ITS USE
- (54) Titre: LAMININE 2 ET SES METHODES D'UTILISATION

# (57) Abstract

The present invention provides substantially purified laminin 2, methods for making recombinant laminin 2, cells that express recombinant laminin 2, and methods for using the substantially purified laminin 2 to accelerate peripheral nervous system nerve regeneration, and to promote cell attachment and migration.

## (57) Abrégé

La présente invention concerne une laminine 2 sensiblement purifiée, des méthodes de construction d'une laminine 2 de recombinaison, des cellules exprimant ladite laminine 2 de recombinaison, ainsi que des méthodes d'utilisation de la laminine 2 sensiblement purifiée visant à accélérer la régénération des nerfs du système nerveux périphérique et à favoriser la fixation et la migration cellulaires.

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# Description

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#### LAMININ 2 AND METHODS FOR ITS USE

#### 5 Cross Reference

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This application claims priority to U.S. Provisional Patent Application Serial Nos. 60/131,720 filed April 30, 1999; 60/139,198 filed June 15, 1999; and 60/143,289 filed July 12, 1999; 60/155,945 filed September 24, 1999; all of which are incorporated herein by reference in their entirety.

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Field of the Invention

function.

This application relates to recombinant laminin 5 and methods for its use.

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## **Background of the Invention**

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Basal laminae (basement membranes) are shect-like, cell-associated extracellular matrices that play a central role in cell growth, tissue development, and tissue maintenance. They are present in virtually all tissues, and appear in the earliest stages of embryonic development.

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Basal laminae are central to a variety of architectural and cell-interactive functions (See for example, Malinda and Kleinman, Int. J. Biochem. Cell Biol. 28:957-959 (1996); Aumailley and Krieg, J. Invest. Dermatology 106:209-214 (1996)). For example:

 They serve as architectural supports for tissues, providing adhesive substrata for cells.

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2. They create perm-sclective barriers between tissue compartments that impede the migration of cells and passively regulate the exchange of macromolecules. These properties are illustrated by the kidney glomerular basement membrane, which functions as an important filtration structure, creating an effective blood-tissue barrier that is not permeable to most proteins and cells.

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Basal laminae create highly interactive surfaces that can promote cell migration
and cell elongation during embryogenesis and wound repair. Following an injury,
they provide a surface upon which cells regenerate to restore normal tissue

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4. Basal laminae present information encoded in their structure to contacting cells that is important for differentiation and tissue maintenance. This information is communicated to the cells through various receptors that include the integrins, dystroglycan, and cell surface proteoglycans. Signaling is dependent not only on the presence of matrix ligands and corresponding receptors that interact with sufficient affinities, but also on such topographical factors as ligand density in a three-dimensional matrix "landscape", and on the ability of basal lamina components to cluster receptors. Because these matrix proteins can be long-lived, basal laminae create a "surface memory" in the basal lamina for resident and transient cells.

The basal lamina is largely composed of laminin and type IV collagen heterotrimers that in turn become organized into complex polymeric structures. To date, six type IV collagen chains and at least twelve laminin subunits have been identified. These chains possess shared and unique functions and are expressed with specific temporal (developmental) and spatial (tissue-site specific) patterns.

Laminins are a family of heterotrimeric glycoproteins that reside primarily in the basal lamina. They function via binding interactions with neighboring cell receptors, and by forming laminin networks, and they are important signaling molecules that can strongly influence cellular function. Laminins are important in both maintaining cell/tissue phenotype as well as promoting cell growth and differentiation in tissue repair and development.

Laminins are large, multi-domain proteins, with a common structural organization. The laminin molecule integrates various matrix and cell interactive functions into one molecule.

Laminin molecules are comprised of an  $\alpha$ -,  $\beta$ -, and  $\gamma$ -chain subunit joined together through a coiled-coil domain. Within this structure are identifiable domains that possess binding activity towards other laminin and basal lamina molecules, and membrane-bound receptors. Domains VI, IVb, and IVa form globular structures, and domains V, IIIb, and IIIa (which contain cysteine-rich EGF-like elements) form rod-like structures. (Kamiguchi et al., Ann. Rev. Neurosci. 21:97-125 (1998)) Domains I and II of the three chains participate in the formation of a triple-stranded coiled-coil structure (the long arm).

Table 1 shows the individual chains that each laminin type is composed of:

TABLE 1. Known laminin family members

Protein	Chains
Laminin-1	α1β1γ1
Laminin-2	α2β1γ1
Laminin 3	α1β2γ1
Laminin-4	α2β2γ1
Laminin-5	α3β3γ2
Laminin-6	α3β1γ1
Laminin-7	α3β2γ1
Laminin-8	α4βίγί
Laminin-9	α4β2γ1
Laminin-10	α5β1γ1
Laminin –11	α5β2γ1
Laminin-12	α2β1γ3

Four structurally-defined family groups of laminins have been identified. The first group of five identified laminin molecules all share the  $\beta 1$  and  $\gamma 1$  chains, and vary by their  $\alpha$ -chain composition ( $\alpha 1$  to  $\alpha 5$  chain). The second group of five identified laminin molecules all share the  $\beta 2$  and  $\gamma 1$  chain, and again vary by their  $\alpha$ -chain composition. The third group of identified laminin molecules has one identified member, laminin 5, with a chain composition of  $\alpha 3\beta 3\gamma 2$ . The fourth group of identified laminin molecules has one identified member, laminin 12, with the newly identified  $\gamma 3$  chain ( $\alpha 2\beta 1\gamma 3$ )

Some progress has been made in elucidating the relationship between domain structure and function. (See, for example, Wewer and Engvall, Neuromusc. Disord. 6:409-418 (1996).) The overall sequence similarity among the homologous domains in different chains varies, but it is highest in domain VI (thought to play a key role in laminin polymerization), followed by domains V (possibly involved in protein-protein interactions) and III (entactin/nidogen binding; possible cell adhesion sites), and is lowest in domains I, II (both thought to be involved in intermolecular assembly, and containing possible cell adhesion sites), and G. Not all domains are present in all 3 types of chains. The globular G domain (thought to be involved in cell receptor binding) is present only in the  $\alpha$  chains. Other domains may not be present in all chains within a certain chain type. For example, domain VI is absent from  $\alpha$ 3,  $\alpha$ 4, and  $\gamma$ 2 chains. (Wewer and Engvall, 1996)

As a result of their large size (>600 kD) and unique structure, laminin molecules can be resolved in the electron microscope. (Wewer and Engvall, 1996) Typically, laminins appear as cross-shaped molecules in an electron micrograph. The three short arms of the cross represent the amino terminal portions of each of the three separate laminin chains (one short arm per chain). The long arm of the cross is composed of the C-terminal parts of the three chains, which together form a coiled coil structure. (Wewer and Engvall, 1996) The long arm ends with the globular G domain.

The coiled-coil domain of the long arm is crucial for assembly of the three chains of laminin. (Yurchenco et al., Proc. Natl. Acad. Sci. 94:10189-10194 (1997)). Disulfide bonds bridge and stabilize all three chains in the most proximal region of the long arm and join the  $\beta$  and  $\gamma$  chains in the most distal region of the long arm.

A model of laminin receptor-facilitated self-assembly, based on studies conducted with cultured skeletal myotubes and Schwann cells, predicts that laminins bind to their receptors, which freely diffuse in a fluidic membrane when ligand-free. Receptor engagement forces the laminins into a high local two-dimensional concentration, facilitating their mass-action driven assembly into ordered surface polymers. In this process, the engaged receptors are also reorganized, accompanied by cytoskeletal rearrangements. (Colognato, J. Cell Biol. 145:619-631 (1999)) This reorganization activates the receptors, causing signal transduction with the alteration of cell expression, shape and/or behavior.

One class of laminin receptors are the integrins, which are cell surface receptors that mediate many cell-matrix and cell-cell interactions. Integrins are heterodimers, consisting of an  $\alpha$  and a  $\beta$  subunit. 16  $\alpha$ - and 8  $\beta$ -subunits are known, and at least 22 combinations of  $\alpha$  and  $\beta$  subunits have been identified to date. Some integrins have only one or a few known ligands, whereas others appear to be very promiscuous. Binding to integrins is generally of low affinity, and is dependent on divalent cations. Integrins, activated through binding to their ligands, transduce signals via kinase activation cascades, such as focal adhesion and mitogen-activated kinases. Several different integrins bind different laminin isoforms more or less specifically. (Aumailley et al., In The Laminins, Timpl and Ekblom, eds., Harwood Academic Publishers, Amsterdam. pp. 127-158 (1996))

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Laminin 2 is composed of  $\alpha 2$  (400 kD),  $\beta 1$  (approximately 100 kD), and  $\gamma 1$  (approximately 100 kD) chains. The C-terminal G domain of the  $\alpha 2$  chain forms a large globular structure responsible for binding to  $\alpha$ -dystroglycan. (Kamiguchi et al., 1998).

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The short arm domains of laminin 1 are involved in the self-aggregation process (Schittney and Yurchenco, J. Cell Biol. 110:825-832 (1990)) and with extracellular matrix components, such as type IV collagen. Homology between the  $\alpha$ 1 (laminin 1) and  $\alpha$ 2 chains is 58.6%. The significant homology between the  $\alpha$ 1 and  $\alpha$ 2 chains, especially in the N-terminal domains, and their identical  $\beta$  and  $\gamma$  chains, suggest that laminin 2 has a similar structural organization to laminin 1. (Kamiguchi et al., 1998)

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Laminin 2 was originally found in the basement membranes of the placenta, striated muscle, and Schwann cells. (Leivo and Engvall, Proc. Natl. Acad. Sci. USA 85:1544-1548 (1998)) In normal adults, laminin 2 is predominant in the basal lamina of skeletal muscle, where it serves to provide mechanical reinforcement to the sarcolemma by linking the extracellular matrix and the subsarcolemmal cytoskeleton. (Sancs et al., J. Cell Biol. 111:1685-1699 (1990))

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Genetic defects affecting the structure or expression of laminin 2 are the causes of a major type of congenital muscular dystrophy (CMD). Laminin 2 has been shown to be specifically required for stabilizing myotubes during skeletal muscle development,

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and for preventing apoptosis, which is believed to explain some of the pathological events observed in CMD. (Kamiguchi et al., 1998)

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In vitro studies have demonstrated that partially purified laminin 2 is important for myotube survival and maintenance of phenotype. (Vachon et al., J. Cell Biol. 134:1483-1497 (1996)) In vivo experiments have shown partial laminin  $\alpha 2$  chain restoration in a laminin  $\alpha 2$  deficient, CMD animal model by primary muscle cell transplantation. (Vilquin et al., J. Cell Biol. 133:185-197)

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Laminin 2 is also the predominant laminin isoform present in the endoneurial basement membrane of developing and mature peripheral nerves, and was shown to promote Schwann cell migration, neurite outgrowth, and neurite regeneration (Kamiguchi et al., 1998), as well as myelin formation by oligodendrocytes (Buttery et al., Mol. Cell. Neurosci. 14:199-212 (1999). The results of various experiments have indicated that laminin 2, rather than laminin 1, is important in Schwann cell/basal lamina interactions, especially at early developmental stages. (Kamiguchi et al., 1998) Other

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studies have demonstrated that partially purified laminin 2 promotes neuronal cell migration and axon outgrowth (Agius and Cochard, J. Neurosci. 18:328-338 (1998); Kamiguchi et al, 1998; U.S. Patent Nos. 5,444,158; 5,872,231; 5,624,905; and 5,863,743; Bates and Meyer, Develop. Biol. 181:91-101 (1997)). In a laminin 2 deficient CMD animal model, CMD was accompanied by dysmyelination of peripheral motor nerves, indicating that laminin 2 plays an important role in peripheral myelinogenesis.

Partially purified laminin 2 has also been shown to promote cell migration and attachment to a substrate of a variety of cell types, particularly muscle cells and cells of neuronal origin. (U.S. Patent No. 5,444,158; White et al., Am. J. Resp. Biol. 20:787-796 (1999); Engvall et al., Exp. Cell Res. 198:115-123 (1992))

It has also been demonstrated that the molecular basis of the neural tropism of *Mycobacterium leprae* is attributable to the specific binding of *M. leprae* to the G domain of the laminin α2 chain on Schwann cell-axon units, while α-dystroglycan (αDG) was shown to serve as a Schwann cell receptor for *M. leprae*. (Rambukkana et al., Science 282:2076-2079 (1998); Rambukkana et al., Cell 88:811-821 (1997)). Native αDG was shown to competitively inhibit the laminin-2 mediated M. leprae binding to primary Schwann cells. (Rambukkana et al. 1998)

Thus, research and therapeutic applications for laminin 2 and fragments thereof include, but are not limited to, peripheral nervous system (PNS) nerve regeneration, treatment of degenerative muscle disorders, regulating angiogenesis, promoting cell attachment and migration, ex vivo cell therapy, improving the biocompatibility of medical devices, improving the "take" of grafts, and preparing improved cell culture devices and media.

At present, there is not a means to isolate adequate substantially purified laminin 2 from cell or tissue sources for research or therapeutic purposes, nor has a means been developed for production of recombinant heterotrimeric laminin 2. Laminin 2 can be partially purified from either placenta, or, in lesser amounts, from skeletal muscle. Human placenta has provided the only source for obtaining up to several milligrams of protein. (Cheng et al., J. Biol. Chem. 272:31525-32, 1997) However preparations of this laminin normally contain about an equal molar quantity of laminin 4 ( $\alpha 2\beta 2\gamma 1$ ) and the protein nidogen (entactin). The nidogen is bound to the laminin through a fairly strong but non-

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additional steps, a significant contaminating level of laminin 4 remains. Denaturing conditions are required to remove the nidogen.

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Therefore, there is a need in the art for adequate amounts of substantially purified laminin-2, and methods for making laminin 2. A preferred method of production is the use of recombinant DNA technology to engineer a cell line of choice to produce recombinant laminin-2. A recombinant-based method of laminin-2 production has several advantages over purification from tissue or isolation from cell lines in culture:

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1. The recombinantly produced protein is free of pathogens. While this is also true for endogenous cell culture produced protein, protein derived from human tissue carries a risk for contamination by HIV, hepatitis, and other infectious agents.

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2. Expression levels of the protein, and hence yields, can be improved through the use of genetically engineered genes/vectors that enhance the production of the encoded protein.

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3. It is possible to engineer additional peptide sequences to the protein chain that provides a binding site for a commercially viable affinity purification procedure.

The method can provide for the modification of protein structure/function

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through the addition, substitution, elimination, and/or other modifications of protein domain structures. For example, it may be desirable to introduce an integrin binding site (e.g. RGD), switch integrin recognition sites, or engineer in a stable binding site to a synthetic substrate. Thus, the creation of expression vectors that express laminin chains generates enormous flexibility for future uses and creates a basis for creating second generation "designer" laminins.

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## **Summary of the Invention**

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The present invention fulfills the need in the art for substantially purified laminin 2 protein, methods for making substantially purified recombinant laminin 2 (hereinafter referred to as r-laminin 2), and methods of using substantially purified laminin 2 for research and therapeutic purposes including, but not limited to, peripheral nerve regeneration, treatment of degenerative muscle disorders, angiogenesis regulation, promoting cell attachment and migration, ex vivo cell therapy, improving the "take" of

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grafts, improving the biocompatibility of medical devices, and preparing improved cell culture devices and media

In one aspect, the present invention provides mammalian cells that have been transfected with expression vector(s) encoding at least one of the laminin  $\alpha 2$ ,  $\beta 1$  and  $\gamma 1$  chains, wherein the cells secrete r-laminin 2.

In another aspect, the present invention provides substantially purified laminin 2 and methods for producing r-laminin 2.

In a further embodiment, the present invention provides a novel, isolated laminin 2  $\alpha$ 2 nucleic acid and  $\alpha$ 2 protein. In this embodiment, the protein product contains an additional 30 amino acids at its carboxyl terminus relative to the previously reported sequence.

In a further aspect, the present invention provides pharmaceutical compositions, comprising substantially purified laminin 2, or the novel recombinant  $\alpha 2$  protein together with a pharmaceutically acceptable carrier. Such pharmaceutical compositions can optionally be provided with other compounds, such as extracellular matrix components.

The present invention further provides methods for peripheral nerve regeneration, treatment of degenerative muscle disorders, regulating angiogenesis, promoting cell attachment and migration, ex vivo cell therapy, improving the biocompatibility of medical devices, improving the "take" of grafts, and preparing improved cell culture devices and media, comprising providing an amount effective of the substantially purified laminin 2, or pharmaceutical compositions thereof, for the desired outcome.

In a further aspect, the present invention provides improved medical devices or grafts, wherein the improvement comprises applying to the devices or grafts an amount effective of substantially purified laminin 2 or pharmaceutical compositions thereof, for the desired application. Such devices can optionally be provided with other compounds, such as extracellular matrix components to further improve the biocompatibility or the effectiveness of the medical device or graft.

In a further aspect, the invention provides improved cell culture devices, by providing an amount effective of substantially purified laminin 2, or pharmaceutical compositions thereof, for the attachment of cells to a cell culture device for the subsequent proliferation/differentiation/stasis of the cells.

In another aspect, the invention provides a cell culture growth supplement, comprising substantially purified laminin 2. In another aspect, the invention provides an

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improved cell culture growth media, wherein the improvement comprises the addition of substantially purified laminin 2 to the growth medium.

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## **Brief Description of the Figures**

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Figure 1 is a photograph of an Coomassie blue-stained SDS-polyacrylamide gel of recombinant laminin 2 compared to laminin 1.

Figure 3 is an immunoblot demonstrating the co-polymerization of laminin 2.

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Figure 2 is an electron micrographs of purified recombinant laminin 2.

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Figure 4 is a graph demonstrating C2C12 myoblast adherence to recombinant laminin 2.

Figure 5 shows the correct sequence of the laminin  $\alpha 2$  cDNA and deduced amino acid sequence.

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#### **Detailed Description of the Preferred Embodiments**

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All references, patents and patent applications are hereby incorporated by reference in their entirety.

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Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression* 

Technology (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in Methods in Enzymology (M.P.

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Deutsheer, ed., (1990) Academic Press, Inc.); PCR Protocols: A Guide to Methods and Applications (Innis, et al. 1990. Academic Press, San Diego, CA), Culture of Animal Cells: A Manual of Basic Technique, 2<sup>nd</sup> Ed. (R.I. Freshney. 1987. Liss, Inc. New York,

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NY), Gene Transfer and Expression Protocols, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.), and the Ambion 1998 Catalog (Ambion, Austin, TX).

As used herein, "laminin 2" includes both r-laminin 2 and laminin 2 substantially purified from tissue sources.

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As used herein, the term "r-laminin 2" refers to recombinant laminin 2, expressed by a cell that has been transfected with one or more expression vectors comprising at least one nucleic acid sequence encoding a laminin 2 chain selected from the  $\alpha$ 2,  $\beta$ 1 and  $\gamma$ 1 chains, processed forms thereof, or other portions thereof that are capable of forming a

heterotrimeric laminin 2 and maintaining laminin 2 activity. Such r-laminin 2 can thus comprise  $\alpha 2$ ,  $\beta 1$ , and  $\gamma 1$  sequences from a single organism, or from different organisms. Laminin 2 chain DNA sequences and their encoded proteins from a variety of organisms are known in the art. (See, for example, Vuolteenaho et al., J. Biol. Chem. 265:15611-15616 (1990); Kallunki et al., J. Biol. Chem. 266:221-228 (1991); Pikkarainen et al., J. Biol. Chem. 263:6751-6758 (1988); Sasaki and Yamada, J. Biol. Chem. 262:17111-17117 (1987); Sasaki et al., Proc. Natl. Acad. Sci. 84:935-939 (1987); Pikkarainen et al., J. Biol. Chem. 262:10454-10462 (1987); and Bernier et al., Matrix Biol. 14:447-455 (1995), all references incorporated by reference herein in their entirety).

The invention encompasses those laminin molecules wherein one or two of the chains that make up the recombinant heterotrimeric laminin 2 are encoded by endogenous laminin 2 chains. In a preferred embodiment, r-laminin 2 is produced by cells that are transfected with one or more expression vectors comprising nucleic acid sequences encoding each of mammalian  $\alpha 2$ ,  $\beta 1$  and  $\gamma 1$  chains, processed forms thereof, or other portions thereof that are capable of forming a heterotrimeric laminin 2 and maintaining laminin 2 activity.

In the present invention, laminin 2 is a secreted protein, which is capable of being directed to the ER, secretory vesicles, and the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Such processing event can be variable, and thus may yield different versions of the final "mature protein". The substantially purified laminin 2 of the present invention includes heterotrimers comprising both the full length and any such processed laminin 2 chains.

As used herein, the term "substantially purified" means that the laminin 2 so designated has been separated from its in vivo cellular environment.

As used herein, a laminin 2 polypeptide chain refers to a polypeptide chain according to one or more of the following:

- (a) comprises a polypeptide structure selected from the group consisting of:
  - 1. R1-R2-R3
  - 2. R1-R2-R3(e)
  - 3. R3

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R3(e)

4.

•		5. R1-R3						
		6. R1-R3(e)						
		7. R2-R3						
10	. 5	8. R2-R3(e)						
		wherein R1 is a amino terminal methionine; R2 is a signal sequence that is						
		capable of directing secretion of the polypeptide, wherein the signal sequence may be the						
15	natural signal sequence for the particular laminin chain, that of another secreted protein							
70		an artificial sequence; R3 is a secreted laminin chain selected from $\alpha 2$ , $\beta 1$ , and $\gamma 1$ chains;						
	and R3(c) is a secreted laminin chain selected from the $\alpha$ 2, $\beta$ 1, and $\gamma$ 1 chains that further							
		comprises an epitope tag (such as those described below), which can be placed at any						
20		position within the laminin chain amino acid sequence; and/or						
		(b) is encoded by a polynucleotide that is substantially similar to on or more of the						
		disclosed laminin chain polynucleotide sequences (SEQ ID NOS.: 1, 3, 5, 7, 9, 11, 13, 15,						
25	15	17, 19, 21, 23, 25, 27, 29, 31) or fragments thereof; and/or						
25		(c) is encoded by a polynucleotide that hybridizes under high or low stringency						
	conditions to coding regions, or portions thereof, of one or more of the recombi							
		laminin 2 chain DNA sequences disclosed herein (SEQ ID NOS.: 1, 3, 5, 7, 9, 11, 13, 15,						
30		17, 19, 21, 23, 25, 27, 29, 31) fragments thereof, or complementary sequences thereof;						
	20	and/or						
		(d) has at least 70% identity to one or more of the disclosed laminin 2 polypeptide						
25		chain amino acid sequences (SEQ ID NOS.: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26,						
35		28, 30, 32, or fragments thereof), preferably at least 80% identity, and most preferably at						
		least about 90% identity.						
	25	The phrase "substantially similar" is used herein in reference to polynucleotide or						
40		polypeptide sequences having one or more conservative variations from the laminin 2						
		sequences disclosed herein, including but not limited to deletions, insertions, inversions,						
		repeats, and substitutions, wherein the resulting laminin chain is functionally equivalent to						
		those disclosed herein.						
45	30	For example, conservative polynucleotide variants may contain alterations in the						
		coding regions, non-coding regions, or both. Especially preferred are polynucleotide						
		variants containing alterations which produce silent substitutions, additions, or deletions,						
50		but do not alter the amino acid sequence of the encoded polypeptide. Nucleotide variants						
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produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, including but not limited to optimizing codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring conservative variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wilcy & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring conservative variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, conservative polynucleotide variants may be generated to improve or alter the characteristics of the expressed laminin chain polypeptides. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein. (See, for example, Ron et al., J. Biol. Chem. 268: 2984-2988 (1993); Dobeli et al., J. Biotechnology 7:199-216 (1988)) Ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. (See, for example, Gayleet al., J. Biol. Chem 268:22105-22111 (1993)) Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained.

Guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, "substantially similar" polypeptides of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be "substantially similar" according to the present invention.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

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"Stringency of hybridization" is used herein to refer to conditions under which nucleic acid hybrids are stable. The invention also includes nucleic acids that hybridize under high stringency conditions (as defined herein) to all or a portion of the coding sequences of the laminin chain polynucleotides disclosed herein, or their complements. The hybridizing portion of the hybridizing nucleic acids is typically at least 50 nucleotides in length. As known to those of skill in the art, the stability of hybrids is reflected in the melting temperature (T<sub>M</sub>) of the hybrids. T<sub>M</sub> decreases approximately 1-1.5°C with every 1% decrease in sequence homology. In general, the stability of a hybrid is a function of sodium ion concentration and temperature. Typically, the hybridization reaction is performed under conditions of lower stringency, followed by washes of varying, but higher, stringency. Reference to hybridization stringency relates to such washing conditions. Thus, as used herein, high stringency refers to an overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

Also contemplated are laminin 2-encoding nucleic acid sequences that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

As used herein, "percent identity" of two amino acids or of two nucleic acids is

determined using the algorithm of Karlin and Altschul (Proc. Natl. Acad. Sci. USA 87:2264-2268, 1990), modified as in Karlin and Altschul (Proc. Natl. Acad. Sci. USA 90:5873-5877, 1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al. (J. Mol. Biol. 215:403-410, 1990). BLAST nucleotide searches are performed with the NBLAST program, score = 100, wordlength = 12, to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches are performed with the XBLAST program, score = 50, wordlength = 3, to obtain an amino acid sequence homologus to a polypeptide of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST is utilized as described in Altschul et al. (Nucleic Acids. Res. 25:3389-3402, 1997). When utilizing BLAST and Gapped BLAST programs, the default paramaters of the respective

Further embodiments of the present invention include polynucleotides encoding laminin 2 chain polypeptides having at least 70% identity, preferably at least 80% identity, and most preferably at least 90% identity to one or more polypeptide sequence contained in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or fragments thereof.

programs (e.g., XBLAST and NBLAST) are used. See http://www.ncbi.nlm.nih.gov.

As used herein, "α2 polynucleotide" refers to a polynucleotide encoding an α2 laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) the nucleotides of said polynucleotide may encode an amino acid sequence substantially similar to one or more of the amino acid sequences set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12 or fragments thereof; (b) polynucleotides that encode polypeptides which share at least 70% identity, preferably 80% identity, and most preferably at least 90% identity with one or more of the sequences set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12, or fragments thereof; (c) the α2 polynucleotides hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 1, 3, 5, 7, 9, 11, fragments thereof, or complementary sequences thereof; or (d) the α2 polynucleotides may encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(c); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted α2 chain polypeptides.

As used herein, "β1 polynucleotide" refers to polynucleotides encoding a β1 laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) the nucleotides of said polynucleotide may encode a polypeptide substantially similar to one or more of the amino acid sequences set forth in SEQ ID NO: 14, 16, 18, 20, or fragments thereof; (b) polynucleotides that encode polypeptides which share at least 70% identity, preferably at least 80%, and most preferably at least 90% identity with one or more of the sequences set forth in SEQ ID NO: 14, 16, 18, 20, or fragments thereof; (c) the β1 cDNAs hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 13, 15, 17, 19, fragments thereof, or complementary sequences thereof; or (d) the β1 polynucleotides may encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(c); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted β1 chain polypeptides.

As used herein, "γ1 polynucleotide" refers to polynucleotides encoding a γ1 laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) the nucleotides of said polynucleotide may encode an amino acid that is substantially similar to one or more of the sequences set forth in SEQ ID NO: 22, 24, 26, 28, 30, 32, or fragments thereof; (b) polynucleotides that encode polypeptides which share at least 70% identity, preferably at least 80%, and most preferably at least 90% identity with one or more of the sequences set forth in SEQ ID NO: 22, 24, 26, 28, 30, 32, or fragments thereof; (c) the γ1 polynucleotides hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 21, 23, 25, 27, 29, 31, fragments thereof, or complementary sequences thereof; or (d) the γ1 polynucleotides may encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted γ1 chain polypeptides.

As used herein, the term "epitope tag" refers to a polypeptide sequence that is expressed as part of a chimeric protein, where the epitope tag serves as a recognition site for binding of antibodies generated against the epitope tag, or for binding of other molecules that can be used for affinity purification of sequences containing the tag.

As used herein, the term "increased biocompatibility" refers to reduced induction of acute or chronic inflammatory response, and reduced disruption of the proper differentiation of implant-surrounding tissues for laminin 2-coated biomaterials relative to an analogous, non-coated biomaterial.

In one aspect, the present invention provides r-laminin 2 expressing-cells that have been transfected with an expression vector containing promoter sequences that are operatively linked to nucleic acid sequences encoding at least one polypeptide sequence comprising the  $\alpha 2$ ,  $\beta 1$  and  $\gamma 1$  chains of laminin 2, or fragments thereof, wherein the transfected cells secrete heterotrimeric laminin 2 containing the recombinant laminin chain. In a preferred embodiment, the cells are transfected with recombinant expression vectors containing promoter sequences that are operatively linked to nucleic acid sequences encoding polypeptide sequences comprising each of the mammalian  $\alpha 2$ ,  $\beta 1$  and  $\gamma 1$  chains of laminin 2, or fragments thereof. After the transfection(s), the cells express each of the recombinant laminin 2 chains, which form the heterotrimer, before r-laminin 2 secretion into the media.

In a preferred embodiment, cDNAs encoding  $\alpha 2$ ,  $\beta 1$  and  $\gamma 1$  laminin chains, or fragments thereof, are subcloned into an expression vector. Alternatively, laminin 2  $\alpha 2$ ,  $\beta 1$  and/or  $\gamma 1$  genomic sequences, including one or more introns, can be used.

Any cell capable of expressing and secreting the r-laminin 2 can be used. Preferably, eukaryotic cells are used, and most preferably mammalian cells are used, including but not limited to kidney and epithelial cell lines. In a most preferred embodiment, the mammalian cells do not express all of the laminin 2 chains endogenously. Carbohydrate and disulfide post-translational modifications are believed to be required for laminin 2 protein folding and function. This makes the use of eukaryotic cells preferable for producing functional r-laminin 2, although other systems are useful for obtaining, for example, antigens for antibody production.

"Recombinant expression vector" includes vectors that operatively link a nucleic acid coding region or gene to any promoter capable of effecting expression of the gene product. The promoter sequence used to drive expression of the individual chains or r-laminin 2 may be constitutive (driven by any of a variety of promoters, including but not limited to, CMV, SV40, RSV, actin, EF) or inducible (driven by any of a number of inducible promoters including, but not limited to, tetracycline, ecdysone, steroid-

responsive). The expression vector must be replicable in the host organisms either as an episome or by integration into host chromosomal DNA. In a preferred embodiment, the expression vector comprises a plasmid. However, the invention is intended to include other expression vectors that serve equivalent functions, such as viruses.

In one embodiment, at least one of the laminin chain polynucleotide sequences, or fragments thereof, is operatively linked to a nucleic acid sequence encoding an "epitope tag", so that at least one of the chains is expressed as a fusion protein with an expressed epitope tag. The epitope tag may be expressed as the amino terminus, the carboxy terminus, or internal to any of the polypeptide chains comprising r-laminin 2, so long as the resulting r-laminin 2 remains functional. Any epitope tag may be utilized, so long as it can be used as the basis for affinity purification of the resulting r-laminin 2. Examples of such epitope tags include, but are not limited to FLAG (Sigma Chemical, St. Louis, MO), myc (9E10) (Invitrogen, Carlsbad, CA), 6-His (Invitrogen; Novagen, Madison, WI), and HA (Boehringer Manheim Biochemicals).

In another embodiment, one of the r-laminin 2 chains is expressed as a fusion protein with a first epitope tag, and at least one other r-laminin chain is expressed as a fusion protein with a second epitope tag. This simplifies the purification procedure and facilitates higher recoveries. Alternatively, the same epitope tag can be used to create fusion proteins with more than one of the r-laminin chains.

In a further embodiment, the epitope tag can be engineered to be cleaveable from the r-laminin 2 chain(s). Alternatively, no epitope tag is fused to any of the r-laminin 2 chains, and the r-laminin 2 is purified by standard techniques, including but not limited to affinity chromatography using antibodies against laminin 2 antibodies or other laminin 2 binding molecules.

Transfection of the expression vectors into eukaryotic cells can be accomplished via any technique known in the art, including but not limited to calcium phosphate co-precipitation, electroporation, or liposome mediated-, DEAE dextran mediated-, polycationic mediated-, or viral mediated transfection. Transfection of bacterial cells can be done by standard methods.

In a preferred embodiment, the cells are stably transfected. Methods for stable transfection and selection of appropriate transfected cells are known in the art. In a most preferred embodiment, a CMV promoter driven expression vector is used in a human kidney embryonic 293 cell line.

In one example, media from cells transfected with a single laminin chain are initially analyzed on Western blots using laminin chain-specific antibodies. The expression of single laminin chains following transfection is generally intracellular. Clones showing reactivity against individual transfected chain(s) are verified by any appropriate method, such as PCR, reverse transcription-PCR, or nucleic acid hybridization, to confirm incorporation of the transfected gene. Preferably, analysis of genomic DNA preparations from such clones is done by PCR using laminin chain-specific primer pairs. Media from transfected clones producing all three chains are further analyzed for r-laminin 2 secretion and/or activity, by any appropriate method, including Western blot analysis and cell binding assays. Activity of the r-laminin 2 is preferably analyzed in cell adhesion and protein binding assays.

In another aspect, the present invention provides substantially purified laminin 2, preferably r-laminin 2. In one embodiment, the substantially purified laminin 2 comprises a first chain comprising an  $\alpha 2$  chain polypeptide; a second chain comprising a  $\beta 1$  chain polypeptide; and a third chain comprising a  $\gamma 1$  chain polypeptide. Alternatively, the r-laminin 2 comprises a first chain that is substantially similar to at least one of the sequences shown in SEQ ID NO: 2, 4, 6, 8, 10, 12 or fragments thereof; a second chain that is substantially similar to at least one of the sequence shown in SEQ ID NO: 12, 14, 16, or 18, or fragments thereof; and a third chain that is substantially similar to the sequence shown in SEQ ID NO: 20, 22, 24, or 26, or fragments thereof.

In another embodiment, the substantially purified r-laminin 2 comprises a first chain comprising a polypeptide that is at least about 70% identical to at least one of the sequences shown in SEQ ID NO: 2, 4, 6, 8, or 10, or fragments thereof; a second chain comprising a polypeptide that is at least 70% identical to at least one of the sequences shown in SEQ ID NO: 14, 16, 18, 20, or fragments thereof; and a third chain comprising a polypeptide that is at least 70% identical to at least one of the sequences shown in SEQ ID NO: 22, 24, 26, 28, 30, 32, or fragments thereof, wherein the first, second, and third polypeptides assemble into a recombinant heterotrimeric laminin 2.

It is preferred that at least one of the first, second, or third chains of the substantially purified human r-laminin 2 is expressed as a fusion protein with an epitope tag.

Alternatively, the r-laminin 2 comprises a heterotrimeric polypeptide structure, wherein each individual chain comprises a general structure selected from the group

consisting of: (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e)

wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or it may be an artificial sequence; R3 is a secreted  $\alpha 2$ ,  $\beta 1$ , or  $\gamma 1$  laminin chain; and R3(e) is a secreted laminin  $\alpha 2$ ,  $\beta 1$ , and  $\gamma 1$  chain that further comprises an epitope tag (such as those described above), which can be placed at any position within the laminin chain amino acid sequence.

In a preferred embodiment, purification of the r-laminin 2 is accomplished by passing media from the transfected cells through an affinity column. For example, antibodies or other binding molecules that bind to a peptide epitope expressed on at least one of the recombinant chains are attached to an affinity column, and bind r-laminin 2 that has been secreted into the media. The r-laminin 2 is removed from the column by passing excess peptide through the column. The eluted protein can subsequently be further purified, if desired.

Eluted fractions are analyzed by any appropriate method, including gel electrophoresis and Western blot analysis. In a further embodiment, the peptide epitope can be cleaved after purification. In other embodiments, two or three separate r-laminin chains are expressed as fusion proteins, each with a different epitope tag, permitting two or three rounds of purification and a doubly or triply purified r-laminin 2. The epitope tag can be engineered so as to be cleavable from the r-laminin 2 chain(s) after purification. Alternatively, no epitope tag is fused to any of the r-laminin 2 chains, and the r-laminin 2 is purified by standard techniques, including but not limited to affinity chromatography using laminin 2 specific antibodies or other laminin 2 binding molecules.

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In another aspect, the present invention provides a novel polynucleotide encoding the laminin  $\alpha 2$  chain, consisting of the sequence shown in SEQ ID NO:1. In another aspect, the present invention provides a novel laminin 2  $\alpha$  polypeptide chain, consisting of the sequence shown in SEQ ID NO:2. These sequences differ from the previously reported sequences, in that the laminin  $\alpha 2$ -chain encoding nucleic acid consists of an extra nucleotide, resulting in the nucleic acid encoding an additional 30 amino acids at the C-terminus over what has previously been reported.

The present invention further provides pharmaceutical compositions comprising substantially purified laminin 2, and a pharmaceutically acceptable carrier. In a preferred embodiment, the pharmaceutical composition comprises substantially purified r-laminin 2. According to this aspect of the invention, other agents can be included in the pharmaceutical compositions, depending on the condition being treated. The pharmaceutical composition may further comprise one or more other compounds, including but not limited to any of the collagens, other laminin types, fibronectin, vitronectin, cadherins, integrins,  $\alpha$ -dystroglycan, entactin/nidogen,  $\alpha$ -dystroglycan, glycoproteins, proteoglycans, heparan sulfate proteoglycan, glycosaminoglycans, epidermal growth factor, vascular endothelial growth factor, fibroblast growth factor, or nerve growth factors, and peptide fragments thereof. In an alternative embodiment, the pharmaceutical compositions comprise the novel laminin  $\alpha$ 2 polypeptide chain of the invention together with a pharmaceutically acceptable carrier.

Pharmaceutical preparations comprising substantially purified laminin 2 can be prepared in any suitable form, and generally comprise the substantially purified laminin 2 in combination with any of the well known pharmaceutically acceptable carriers. The carriers can be injectable carriers, topical carriers, transdermal carriers, and the like. The preparation may advantageously be in a form for topical administration, such as an ointment, gel, cream, spray, dispersion, suspension or paste. The preparations may further advantageously include preservatives, antibacterials, antifungals, antioxidants, osmotic agents, and similar materials in composition and quantity as is conventional. Suitable solutions for use in accordance with the invention are sterile, are not harmful for the proposed application, and may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. For assistance in formulating the compositions of the present invention, one may refer to Remington's Pharmaceutical Sciences, 15th Ed., Mack Publishing Co., Easton, Pa. (1975).

In further aspect, the present invention provides methods and kits for peripheral nerve regeneration, treatment of degenerative muscle disorders, regulating angiogenesis, promoting cell attachment and migration, ex vivo cell therapy, improving the biocompatibility of medical devices, improving the "take" of grafts, and preparing improved cell culture devices and media, comprising providing an amount effective of the

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substantially purified laminin 2, or pharmaceutical compositions thereof for the desired outcome. In all of these methods, the use of r-laminin 2 is preferred.

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As used herein, the term "grafts" refers to both natural and prosthetic grafts as well as implants.

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The treatment of peripheral nerve injuries is a common surgical problem. Nerve injuries can result from trauma, chronic compression, ischemia, radiation, errors of therapy and other causes. The severe forms of injury, in which the nerve is partially or completely disrupted, are difficult or impossible to treat by existing therapies. The basal lamina plays a key role in providing a migration guide for regenerating axons and Schwann cells following such nerve injury. The prognosis for successful regeneration is significantly better if the basement membrane remains intact.

Recently, the feasibility of using basal lamina coated bio-materials as a workable

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graft was demonstrated in a rat model in two studies (Kauppila *et al.*, Exp. Neurol. 123:181-191 (1993); Tong *et al.*, Brain Res. 663:155-162). In the first study, a bovine tendon collagen I graft sheet was impregnated with partially purified, non-recombinant mouse laminin-1, with the cut ends of the rat sciatic nerve (8 mm removed) sutured to the ends of the rolled graft. Function to the affected limb, as judged by electrophysiological and behavioral measurements at 4 months post-operatively, was restored (~60-80% relative to unaffected contralateral nerve) with the laminin graft at a level equivalent to restoring the transected nerve segment. The authors further reported that the laminin graft caused fewer signs of pain. In the second study, the authors created a graft by coating collagen fibrils with purified, non-recombinant laminin and fibronectin, and inserting the modified fibrils in a collagen sleeve. This graft, about 1 cm in length, was again sutured to the proximal and distal end of a transected sciatic nerve. Axonal/Schwann cell growth occurred into the graft with ultimate reattachment with the distal nerve stump. By light and electron microscopy, restoration of essential structural/cellular elements was found in

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The studies of Kauppila *et al.* and Tong *et al.* not only demonstrate the value of basal lamina components in regeneration, but also demonstrate therapeutic feasibility. A similar method for enhancing nerve regeneration using a hollow nerve regeneration conduit coated with type I collagen and purified placental laminin (predominately laminin 1) has also been disclosed. (U.S. Patent No. 5,019,087)

the graft with ultimate resorption of the graft material. The laminin/fibronectin coat was

essential since the collagen fibrils alone were not sufficient to restore the nerve.

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Thus, in one embodiment, the present invention provides methods to promote peripheral nerve regeneration, comprising coating a nerve graft with an amount effective of substantially purified laminin 2, or pharmaceutical compositions thereof, to promote regeneration of the nerve. Laminin 2 is the predominant laminin isoform present in the endoneurial basement membrane of developing and mature peripheral nerves, and was shown to promote neuronal cell migration and regeneration, axon outgrowth, myelin membrane formation by oligodendrocytes, and Schwann cell migration. (Kamiguchi et al., (1998); Agius and Cochard, J. Neurosci. 18:328-338 (1998); U.S. Patent No. 5,444,158; Buttery et al., Mol. Cell. Neurosci. 14:199-212 (1999); Bates and Meyer, Develop. Biol. 181:91-101 (1997)). The present invention provides a plentiful supply of substantially purified laminin 2, or pharmaceutical compositions thereof, for coating nerve grafts, and thereby promoting neuronal and Schwann cell migration, axonal migration, myelin membrane formation, and nerve regeneration. The graft can comprise a nerve graft, or a prosthetic graft. Both bioresorbable and non-resorbable materials have been used in tubes for bridging nerve gaps. (See for example, Nyilas, et al., (Trans. Soc. Biomater., 6, 85, 1983), Molander, et al. (Biomaterials, Vol. 4, pp. 276-280, October, 1983), Colin, et al., (Journal of Dental Research July, 1984, pp. 987-993).

In another embodiment, r-laminin 2 is used to promote the healing of degenerative muscle disorders. Laminin 2 is known to be important for myotube survival and maintenance of phenotype. (Vachon et al., J. Cell Biol. 134:1483-1497 (1996)). In vitro studies have demonstrated that partially purified laminin 2 promotes myoblast fusion and myotube formation. (Vachon et al., J. Cell Biol. 134:1483-1497 (1996)) In vivo experiments have shown partial laminin  $\alpha$ 2 chain restoration in a laminin  $\alpha$ 2 deficient, CMD animal model by primary muscle cell transplantation. (Vilquin et al., J. Cell Biol. 133:185-197 (1996)) Thus, mammalian cells that express r-laminin 2, or the novel laminin  $\alpha$ 2 chain of the invention, can be used for cell therapy, to treat patients with degenerative muscle disorders such as muscular dystrophies that are characterized by a laminin  $\alpha$ 2 deficiency.

Partially purified laminin 2 has also been shown to promote the migration of and attachment to a substrate of a variety of cell types, particularly muscle cells and cells of neuronal or mesenchymal origin. (U.S. Patent No. 5,444,158; White et al., Am. J. Resp. Biol. 20:787-796 (1999); Engvall et al., Exp. Cell Res. 198:115-123 (1992))

Thus, in another embodiment, substantially purified laminin 2, or pharmaceutical compositions thereof, can be added to medical devices, tissue culture plates, grafts, and cell culture media to provide important ligand substrates to maintain and expand primary explanted human tissue cells. This takes advantage of what has been observed by many investigators over the past decade, i.e., basal lamina components, in particular laminins, provide optimal surfaces for the adhesion, spreading, propagation, and maintenance of the differentiated phenotype of a large variety of cells. This property of substantially purified laminin 2 can be exploited to increase the biocompatibility of a medical device, to permit the maintenance of human cells in a laboratory affording time to find a suitable donor, and for the expansion of cell populations for transplantation and somatic gene therapy. Possible target cells for *ex vivo* therapy include cells of muscle and neuronal origin, lymphocytes and cells of the immune system, pancreatic islet, parathyroid, adrenal, pituitary, hepatic, cardiac muscle and stem cells.

In another embodiment, the present invention provides methods for regenerating cells and tissues both in vivo and ex vivo. Many of the current approaches for tissue engineering begin with a collagen/polymer scaffolding that is seeded with appropriate cells that can proliferate and differentiate into cell masses and tissue sub-structures. In the development of these methods, attempts have been made to add coatings to the scaffolding to provide for a more natural surface for cell interactions, with the expectation that cell proliferation and tissue development would be enhanced. Coating these matrices with the substantially purified laminin 2 provides for a natural ligand interactive surface to promote normal cell adherence, cell growth and tissue development. Thus, the availability of substantially purified laminin 2 is expected to significantly improve tissue regeneration procedures.

Laminins, or cell extracts containing laminins, have been shown to regulate angiogenesis in a biphasic manner. (See, for example, Nicosia et al., Dev. Biol. 164:197-206 (1994); Bonfil et al., Int. J. Cancer 58:233-239 (1994)). At lower concentrations (30-300 µg/ml), a laminin-entactin complex stimulated angiogenesis in a three-dimensional culture, while at 3000 µg/ml the same complex was inhibitory to angiogenesis. Thus, in another aspect, the present invention provides methods for regulating angiogenesis, comprising contacting a tissue or culture substrate with an amount effective of laminin 2 or pharmaceutical compositions thereof to regulate angiogenesis. In one embodiment, the laminin 2 is used to promote angiogenesis by contacting a tissue or culture substrate with

an amount effective of laminin 2 to promote angiogenesis. In another embodiment, the laminin 2 is used to inhibit angiogenesis, by contacting the tissue or culture substrate with an amount effective of laminin 2 to inhibit angiogenesis. An example of culture substrates to be contacted with laminin 2 to regulate angiogenesis are those used for tissue engineering purposes.

In a further aspect, the present invention comprises medical devices with improved biocompatibility, wherein the devices are coated with the substantially purified laminin 2, or pharmaceutical compositions thereof, alone or in combination with other proteins or agents that serve to increase the biocompatibility of the device surface. The coated device stimulates cell attachment and provides for diminished inflammation and/or infection at the site of entry of the appliance.

Preferably, the device is made of or coated with a biocompatible metal that may be either stainless steel or titanium. Alternatively, the device is made of or coated with a ceramic material, or a polymer including but not limited to polyester, polyglycolic acid or a polygalactose-polyglycolic acid copolymer.

One particular use of the present invention is to increase neuronal, skeletal muscle, endothelial or mesenchymal cell adhesion to target surfaces. For example, vascular grafts and stents may be coated with substantially purified laminin 2 to stimulate endothelial cell attachment, and to minimize platelet adhesion to the graft or stent surface. Alternatively, bone or connective tissue grafts or prostheses may be coated with substantially purified laminin 2 to stimulate adhesion of the appropriate cell type and improved efficiency of grafting.

If the device is made of a natural or synthetic biodegradable material in the form of a mesh, sheet or fabric, substantially purified laminin 2 may be applied directly to the surface thereof. Appropriate cells may then be cultured on the matrix to form transplantable or implantable devices, including dental abutment pieces, needles, metal pins or rods, indwelling catheters, colostomy tubes, surgical meshes and any other appliance for which coating with the substantially purified laminin 2 is desirable. Alternatively, the devices may be implanted and cells may be permitted to attach in vivo.

Coupling of the substantially purified laminin 2 may be non-covalent (such as by adsorption), or by covalent means. The device may be immersed in, incubated in, or sprayed with substantially purified laminin 2 or pharmaceutical compositions thereof.

The dosage regimen for various treatments using the substantially purified laminin

2 of the present invention is based on a variety of factors, including the type of injury or condition, the age, weight, sex, medical condition of the individual, the severity of the condition, and the route of administration. Thus, the dosage regimen may vary widely, but can be determined routinely by a physician using standard methods. Laminins are extremely potent molecules, and one or a few molecules per cell could produce an effect. Thus, effective doses in the pico-gram per milliliter range are possible if the delivery is optimized. Laminins are sometimes present in an insoluble form in the basement membrane and have the capability of polymerizing at concentrations as low as about 50 μg/ml, depending on the laminin isoform and the conditions. Laminins can also polymerize into a gel at a concentration of 2-3 mg/ml. Dosage levels of the order of between 1 ng/ml and 10 mg/ml are thus useful for all methods disclosed herein, preferably between about 1 μg/ml and about 3 mg/ml.

The present invention also provides a method for inducing cell attachment to the device (as disclosed above), comprising coating the appliance with substantially purified laminin 2 prior to incubation with cells appropriate for the desired application.

In another aspect of the present invention, substantially purified laminin 2 is used for the culture of cells, including but not limited to neuronal, skeletal muscle, fibroblasts, Schwann cells, cells of mesenchymal origin, and endothelial cells, by contacting the cells with an amount effective of substantially purified laminin 2 to stimulate attachment and proliferation/differentiation/stasis of cells. The substantially purified laminin 2 can either be provided in the cell culture medium, or as a cell culture medium supplement, or may be coated on the surface of a cell growth substrate. In a preferred embodiment, the method further includes contacting the cells with other compounds, including but not limited to any of the collagens, other laminin types, fibronectin, vitronectin, cadherins, entactin/nidogen,  $\alpha$ -dystroglycan, glycoproteins, proteoglycans, heparan sulfate proteoglycan, glycosaminoglycans, epidermal growth factor or nerve growth factors, and peptide fragments thereof.

The cells may comprise primary cells or cell culture cell lines. The methods of this aspect of the invention can be used in vivo, ex vivo, or in vitro.

In a preferred embodiment, r-laminin 2 is used to coat the surface of a substrate, to promote cell adhesion to the substrate, and to stimulate cell proliferation/differentiation/stasis. The substrate used herein may be any desired substrate. For laboratory use, the substrate may be as simple as glass or plastic. For use in

vivo, the substrate may be any biologically compatible material capable of supporting cell growth. Suitable substrate materials include shaped articles made of or coated with such materials as collagen, regenerated collagen, polyglycolic acid, polygalactose, polylactic acid or derivatives thereof; biocompatible metals such as titanium and stainless steel; ceramic materials including prosthetic material such as hydroxylapatite; synthetic polymers including polyesters and nylons; polystyrene; polyacrylates; polytetrafluoroethylene and virtually any other material to which biological molecules can readily adhere.

In a further aspect, the present invention provides cell growth substrates for the adhesion and proliferation of cells in culture, by providing an amount effective of substantially purified laminin 2 for the attachment of cells to a cell culture device for the attachment and subsequent proliferation, differentiation, or stasis of the cells. The substrates may comprise any of the substrates discussed above. Preferably, r-laminin 2 is coated on the surface of the substrate at a concentration of between about 1 ng/ml and about 10 mg/ml, and more preferably 1 ng/ml and about 10 mg/ml.

In another aspect of the present invention, an improved cell culture medium is provided, wherein the improvement comprises addition to the cell culture medium of an effective amount of substantially purified laminin 2 to the cell culture medium to promote the adherence, proliferation, differentiation, or stasis of cells. Any cell culture media that can support the growth of cells can be used with the present invention. Such cell culture media include, but are not limited to Basal Media Eagle, Dulbecco's Modified Eagle Medium, Iscove's Modified Dulbecco's Medium, McCoy's Medium, Minimum Essential Medium, F-10 Nutrient Mixtures, Opti-MEM® Reduced-Serum Medium, RPMI Medium, and Macrophage-SFM Medium or combinations thereof.

The improved cell culture medium can be supplied in either a concentrated (ie: 10X) or non-concentrated form, and may be supplied as either a liquid, a powder, or a lyophilizate. The cell culture may be either chemically defined, or may contain a serum supplement. Culture media is commercially available from many sources, such as GIBCO BRL (Gaithersburg, MD) and Sigma (St. Louis, MO). In an alternative embodiment, the r-laminin 2 is used as a cell culture supplement.

The present invention may be better understood with reference to the accompanying examples that are intended for purposes of illustration only and should not be construed to limit the scope of the invention, as defined by the claims appended hereto.

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### **Examples**

Recombinant Laminin-2

cDNAs coding for the complete open reading frame of the human \$1 chain and the human yl chain have been described. (Kallunki et al., J. Biol. Chem. 266:221-228 (1991); Pikkarainen et al., J. Biol. Chem. 262:10454-10462 (1987); Pikkarainen et al., J. Biol. Chem. 263:6751-6758 (1988); Pikkarainen et al., Eur. J. Biochem. 209:571-582 (1992)). The y1 cDNA was modified to contain a 3' end (corresponding to the C-terminal end) insertion coding for the FLAG peptide epitope tag (SEQ ID NO:25). The complete human laminin a2 cDNA was constructed from the large (approximately 2/3 of open reading frame) cDNA as described in (Vuolteenaho et al., J. Cell Biol. 124:381-394 (1994)) with the C-terminal (3'-end) cDNA as described in (Ehrig et al., Proc. Natl. Acad. Sci. 87:3264-3268 (1990)). The  $\beta$ 1,  $\gamma$ 1, and  $\alpha$ 2 cDNAs were inserted into the pCIS (Genentech, South San Francisco, CA), pRC-CMV, and pCEP4 (InVitrogen, Inc., Carlsbad, CA) mammalian expression vectors respectively. pRC-CMV contained a neo (G418) expression cassette and pCEP4 contained a puromycin expression cassette, each under a separate promoter. Transfection of human embryonic kidney 293 cells (adenovirus transformed, ATCC CRL 1573) with the y1-FLAG expression vector was carried out by calcium phosphate precipitation in 35 mm plastic dishes as previously described (Yurchenco et al., Proc. Natl. Acad. Sci. 94:10189-94 (1997)). Laminin y1 expressing stable clones were selected in the presence of G418 antibiotic. These cells were found to express the laminin y1 chain that reacted with both laminin and FLAGspecific antibodies in immunoblots. One such clone was subsequently co-transfected with the expression vector DNA coding for the a2 and \beta1 laminin chains. New clones were selected in the presence of G418+ puromycin. A clone (designated #44) was determined to express all three laminin 2 chains, by using polyclonal antibodies specific for placental laminin and the α2-G domain, β1 chain, and FLAG epitope tag (Cheng et al., J. Biol. Chem. 272:31525-32 (1997); Rambukkana et al., Cell 88:811-821 (1997)). This clone was expanded in tissue culture. Conditioned serum-containing medium was collected and pooled for purification of sccreted protein.

Purification of recombinant laminin 2

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30 Functional Data

electron microscopy (Figure 2).

Recombinant laminin 2 was found to possess self-assembly activity in a copolymerization assay (Figure 3). A fixed trace amount of r-laminin 2 was mixed with increasing concentrations of laminin 1 in separate tubes (each containing a small amount

The procedure is described for 100 ml of pooled conditioned medium. Purification was carried out at 4°-10°C in a cold room. A small column was packed with two ml of heparin-Sepharose-4B beads and equilibrated with Tris-buffer (50 mM Tris-HCl, pH 7.4, containing 1 MM EDTA and 0.1 mM PMSF) diluted 2:1 with water. The medium was passed through the column. The column was then washed with several volumes of Trisbuffer to decrease the NaCl concentration. One ml of anti-FLAG M2 agarose affinity gel suspension (Sigma-Aldrich, St. Louis, MO) was added to the preparation and used to absorb the recombinant protein bearing the FLAG epitope tag. After washing five times with Tris-buffer, 0.1 mg (in one ml) of FLAG peptides (Sigma-Aldrich) was added to elute the recombinant laminin protein from the beads. The protein was freed of peptides with a spin column. Recombinant protein was characterized by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) (Figure 1), immunoblotting, and Pt/C rotary shadow

Recovered yields of recombinant laminin 2 were 6  $\mu$ g/ml purified protein from conditioned medium (determined from a 100 ml batch preparation). The recombinant laminin had three Coomassie blue-staining bands, the larger corresponding to the  $\alpha 2$  subunit. (Figure 1) Some unprocessed (i.e.: uncleaved)  $\alpha 2$  chain was typically observed. The cleaved version contained a high molecular weight band (approximately 300 kDa) and a 75 kDa band, the latter the predicted G fragment. (Cheng et al., J. Biol. Chem. 272:31525-32 (1997) The two forms of laminin 2 could be separated from each other by heparin affinity chromatography.

Figure 2 is an electron micrograph of purified r-laminin 2, which was dialyzed into 0.15M ammonium bicarbonate, mixed with glycerol to a final ratio of 6:4 glycerol:buffer, and nebulized onto freshly cleraved mica. The sample was evacuated in a Balzars BAF-500K freeze-etch unit and rotary shadowed at an 8° angle with 0.9 nm Pt/C as described (Yurchenco et al., Proc. Natl. Acad. Sci. 94:10189-94 (1997)). As can be seen from the figure, r-laminin 2 demonstrates the cruciform structure that is typical of endogenously expressed laminin molecules.

of bovinc serum albumin (BSA)) and incubated at 37µC as described (Cheng et al., J. Biol. Chem. 272:31525-32 (1997)). The incubation mixtures were then centrifuged in supernatant (S) and polymer pellet (P) fractions. Laminin 2 was detected with FLAG-specific antibody. At higher conentrations, increasing fractions of laminin 2 are detected in the pellet fraction, evidence for laminin-type polymerization.

R-laminin 2 was also found to support adhesion and spreading of C2C12 myoblasts (Figure 4), but not HT1080 fibrosarcoma cells (data not shown). Cultured myoblasts were added to 96-well culture dishes previously coated with two preparations of r-laminin 2 (two left bars), or with r-laminin 2 bearing different deletions of the G domain, all at 5  $\mu$ g/ml. Deletion of G1-3 sub-domains (which bears the  $\alpha$ 7 $\beta$ 1 integrin binding site), or all of G (which also removes the dystroglycan sites) greatly reduced binding.

### Human laminin a2 polynucleotide and polypeptide

We have determined that the published sequence of the human laminin  $\alpha 2$  nucleic acid and protein sequences (Ehrig et al., PNAS 87:3264-3268 (1990) are incorrect. An erroneous dropped G base that should lie near the 3' end of the nucleic acid sequence (Figure 5), leads to a prediction of a prematurely truncated laminin alpha2-G domain. The correct amino acid sequence for the  $\alpha 2$  chain protein is shown in Figure 5.

One of the most serious consequences of the erroneous sequence may be that the end of the G domain is predicted to lack a cysteine residue that is conserved in different laminins, and is present in the corrected sequence presented here. It is thought that this cysteine pairs with another cysteine in the G domain and is important for protein conformation. Furthermore, if the incorrect sequence is used, an epitope tag placed at the apparent C-terminus will in fact be out of frame, and thus the epitope tag will not be functional.

The present invention is not limited by the aforementioned particular preferred embodiments. It will occur to those ordinarily skilled in the art that various modifications may be made to the disclosed preferred embodiments without diverting from the concept of the invention. All such modifications are intended to be within the scope of the present invention.

# Claims

WO 00/66730	PCT/US00/1137

5		We claim
		Substantially purified laminin 2.
10	5	2. The substantially purified laminin 2 of claim 1, comprising recombinant laminin 2.
		3. The substantially purified recombinant laminin 2 of claim 2 comprising:
15		a first chain comprising a polypeptide that is substantially similar to an $\alpha 2$ laminin chain;
	10	a second chain comprising a polypeptide that is substantially similar to a $\beta 1$
		laminin chain; and
20		a third chain comprising a polypeptide that is substantially similar to a $\gamma 1$ laminin
		chain;
		wherein the first, second, and third chains are assembled into recombinant
25	15	heterotrimeric laminin 2.
		4. The substantially purified recombinant laminin 2 of claim 2 comprising:
	,	a first chain encoded by a polynucleotide that hybridizes under high stringency
30		conditions to a coding region of one or more of SEQ ID NO:1, 3, 5, 7, 9, 11, or fragments
	20	thereof;
		a second chain encoded by a polynucleotide that hybridizes under high stringency
		conditions to a coding region of one or more of SEQ ID NO:13, 15, 17, 19 or fragments
35		thereof; and
		a third chain encoded by a polynucleotide that hybridizes under high stringency
	25	conditions to a coding region of one or more of SEQ ID NO: 21, 23, 25, 27, 29, 31 or
40		fragments thereof;
		wherein the first, second, and third chains are assembled into recombinant
		heterotrimeric laminin 2.
45	30	5. The substantially purified recombinant laminin 2 of claim 2 comprising:
		a first chain comprising a polypeptide at least 70% identical to one or more of SEQ
		ID NO:2, 4, 6, 8, 10, 12 or fragments thereof;
50		a second chain comprising a polypeptide at least 70% identical to one or more of

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SEQ ID NO:14, 16, 18, 20 or fragments thereof; and

a third chain comprising a polypeptide at least 70% identical to one or more of SEQ ID NO:22, 24, 26, 28, 30, 32, or fragments thereof;

wherein the first, second, and third chains are assembled into recombinant heterotrimeric laminin 2.

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6. The substantially purified recombinant laminin 2 of claim 2 comprising a first, second, and third polypeptide chain, wherein the first, second, and third polypeptide chains each comprise a general structure selected from the group consisting of: (1) R1-R2-R2-(2) R1-R2-(2) R1-R2-(2) R1-R2-(2) R1-R2-(2) R1-R2-(2) R2-(2) R1-R2-(2) R1-

R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e)

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wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or it may be an artificial sequence; R3 is a secreted  $\alpha$ 2 laminin chain for the first polypeptide chain, a secreted  $\beta$ 1 laminin chain for the second polypeptide chain, and  $\gamma$ 1 laminin chain for the third polypeptide chain; and R3(e) is identical to R3, but further comprises an epitope tag.

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7. Recombinant laminin 2-expressing host cells.

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8. The recombinant laminin 2-expressing host cells of claim 7, wherein the cells express recombinant laminin 2 comprising:

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a first chain comprising a recombinant polypeptide that is substantially similar an laminin  $\alpha 2$  polypeptide;

a second chain comprising a recombinant polypeptide that is substantially similar to a laminin  $\beta 1$  polypeptide sequence; and

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a third chain comprising a recombinant polypeptide that is substantially similar to a laminin y1 polypeptide sequence;

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wherein the cell expresses the first, second, and third chains, and wherein the first, second, and third chains assemble into recombinant laminin 2 that is secreted into the media by the cultured cell.

9. The recombinant laminin 2-expressing host cells of claim 7, wherein the cells 5 express recombinant laminin 2 comprising: a first chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO:1, 3, 5, 7, 9, 11, or fragments 10 5 thereof; a second chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO:1, 15, 17, 19, or fragments thereof; and 15 a third chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO: 21, 23, 25, 27, 29, 31, or fragments thereof; 20 wherein the cell expresses the first, second, and third chains, and wherein the first, second, and third chains assemble into recombinant laminin 2 that is secreted into the media by the cultured cell. 15 25 10. The recombinant laminin 2-expressing host cells of claim 7, wherein the cells express recombinant laminin 2 comprising: a first chain comprising a polypeptide at least 70% identical to one or more of SEQ ID NO:2, 4, 6, 8, 10, 12, or fragments thereof; 30 a second chain comprising a polypeptide at least 70% identical to one or more of 20 SEQ ID NO:14, 16, 18, 20, or fragments thereof; and a third chain comprising a recombinant polypeptide at least 70% identical to one or 35 more of SEQ ID NO:22, 24, 26, 28, 30, 32, or fragments thereof; wherein the cell expresses the first, second, and third chains, and wherein the first, second, and third chains assemble into recombinant laminin 2 that is secreted into the media by the cultured cell. 40 The recombinant laminin 2-expressing host cells of claim 7, wherein the cells 11. express recombinant laminin 2 comprising a first, second, and third polypeptide chain, 45 wherein the first, second, and third polypeptide chains each comprise a general structure selected from the group consisting of: (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e)

wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable 5 of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or it may be an artificial sequence; R3 is a secreted a2 laminin chain for the first polypeptide chain, 10 a secreted \$1 laminin chain for the second polypeptide chain, and y1 laminin chain for the third polypeptide chain; and R3(e) is identical to R3, but further comprises an epitope tag. 12. The host cells of any of claims 7-11, wherein the host cell is a mammalian cell. 15 The host cells of claim 12, wherein at least one of the first, second, or third chains 10 13. is expressed as a fusion protein with an epitope tag. 20 14. A method of purifying recombinant laminin 2, comprising: providing the host cells of claim 12; a. 15 25 b. growing the cells in cell culture medium under conditions to stimulate expression of the recombinant laminin 2 chains; passing the cell culture medium through an affinity chromatography 30 column, wherein the column contains a compound that binds to the recombinant laminin 2; 35 washing the affinity column to remove unbound materials; and đ. eluting the bound recombinant laminin 2 from the column. 25 e. 40 15. Substantially purified recombinant laminin 2 isolated according to the method of claim 14. 45 A pharmaceutical composition comprising: 30 16. a. laminin 2; and a pharmaceutically acceptable carrier. b. 50 34

5		17. The pharmaceutical composition of claim 16, wherein the laminin 2 comprises recombinant laminin 2.
10	5	18. A method to promote nerve regeneration in a mammal, comprising administering to a mammal in need thereof an amount effective of the laminin 2 of any of claims 1-5 and 15 to promote nerve regeneration.
15	10	19. A method for regulating angiogenesis, comprising contacting a tissue in need thereof with an amount effective to regulate angiogenesis of the laminin 2 of any of claims 1-5 and 15 to regulate angiogenesis.
25	. 15	20. A method to improve the biocompatibility of a medical device, comprising contacting the medical device with an amount effective of the laminin 2 of any of claims 1-5 and 15 to improve the biocompatibility of the medical device.
30	20	21. An improved medical device, comprising a medical device with an amount effective of the laminin 2 of any of claims 1-5 and 15 to improve the biocompatibility of the medical device.
35		<ul> <li>A method to promote cell adhesion to a surface, comprising contacting cells with an amount effective of the laminin 2 of any of claims 1-5 and 15 to promote cell adhesion to a surface.</li> <li>An improved cell growth surface, wherein the improvement consists of providing a</li> </ul>
40	25	cell growth surface that has been coated with an amount effective of the laminin 2 of any of claims 1-5 and 15 to promote cell attachment to the cell growth surface.
<b>4</b> 5	30	24. A method to promote nerve regeneration in a mammal, comprising administering to a mammal in need thereof an amount effective of the pharmaceutical composition of claim16 or 17 to promote nerve regeneration.

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25. A method for regulating angiogenesis, comprising contacting a tissue in need thereof with an amount effective to regulate angiogenesis of the pharmaceutical composition of claim 16 or 17 to regulate angiogenesis.

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26. A method to improve the biocompatibility of a medical device, comprising contacting the medical device with an amount effective of the pharmaceutical composition of claim 16 or 17 to improve the biocompatibility of the medical device.

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27. An improved medical device, comprising a medical device with an amount effective of the pharmaceutical composition of claim 16 or 17 to improve the biocompatibility of the medical device.

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28. A method to promote cell adhesion to a surface, comprising contacting cells with an amount effective of the pharmaceutical composition of claim 16 or 17 to promote cell adhesion to a surface.

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29. An improved cell growth surface, wherein the improvement consists of providing a cell growth surface that has been coated with an amount effective of the pharmaceutical composition of claim 16 or 17 to promote cell attachment to the cell growth surface.

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20 30. An isolated recombinant laminin α2 chain polynucleotide consisting essentially of the sequence shown in SEQ ID NO:1.

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31. A substantially purified laminin  $\alpha 2$  chain polypeptide consisting essentially of the sequence shown in SEQ ID NO:2.

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32. An expression vector comprising the polynucleotide of SEQ ID NO:1.

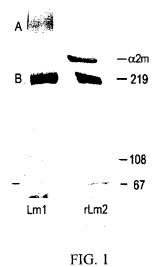
A host cell transfected with the expression vector of claim 32.

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34. A method for treating degenerative muscle disorders in a mammal, comprising administering the host cells of any of claims 7-13 and 33 to a mammal in need thereof, wherein the host cells secrete an amount effective of the recombinant laminin 2 or the recombinant laminin  $\alpha$ 2 chain polypeptide, to treat the degenerative muscle disorder.

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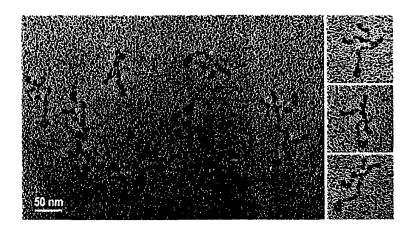


FIG. 2

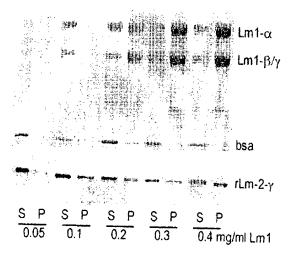


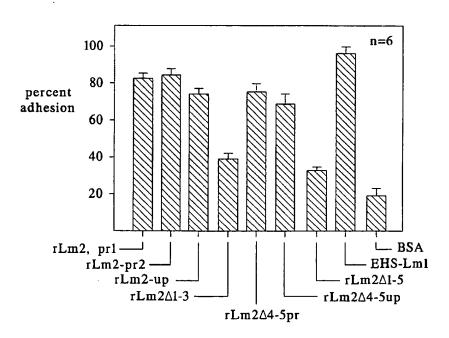
FIG.3

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## FIG. 4

C2C12 myoblasts



Substrate (5 µg/ml)

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$\overline{FIG.5}$	TCAGATCCCT GAAGCTCACC AAAGGCACAG CAAGCCACTG GAGGTTAATT TTGCCAAGGC	AGICTAGGGA CTTCGAGTGG TTTCCGTGTC GTTCGGTGAC CTCCAATTAA AACGGTTCCG	71 81 91 1 11	+3 P W N &	CCTGGAACTG A	GGACCTTGAC T Site of
	RSL KLT KGT ASHW RLI LPR	K L T K G T A S H W R L I GAAGCICACC AAAGGCACAG CAAGCCACTG GAGGTTAAIT	K L T K G T A S H W R L I GAAGCTCACC AAAGGCACAG CAAGCCACTG GAGGTTAATT CTTCGAGTGG TTTCCGTGTC GTTCGGTGAC CTCCAATTAA	K         L         T         K         G         T         A         S         H         W         R         L         I           GAAGCTCACC         AAAGGCACAG         CAAGCCACTG         GAGGTTAATT           CTTCGAGTGG         TTTCCGTGTC         GTTCGGTGAC         CTCCAATTAA           71         81         1	AGATCCCT GAAGCTCACC AAAGGCACAG CAAGCCACTG GAGGTTAATT STCTAGGGA CTTCGAGTGG TTTCCGTGTC GTTCGGTGAC CTCCAATTAA  71 81 1	R         S         L         T         K         G         T         A         S         H         W         R         L         I         L         P         R           CAGATCCCT         GAAGCTCACC         AAAGGCACAG         CAAGCCACTG         GAAGCTTAATT         TTGCCAAGG           STCTAGGGA         CTTCGAGTGG         TTTCCGTGTC         GTTCGGTGAC         CTCCAATTAA         AACGGTTCC           W         N         &         1         11         11           TTGGAACTG         A         1         1         11
12 21 31 41 51		GAAGCICACC AAAGGCACAG CAAGCCACTG GAGGTTAAIT	GAAGCICACC AAAGGCACAG CAAGCCACIG GAGGTIAAIT CITCGAGIGG ITTCCGIGIC GITCGGIGAC CICCAAITAA	GAAGCTCACC AAAGGCACAG CAAGCCACTG GAGGTTAATT CTTCGAGTGG TTTCCGTGTC GTTCGGTGAC CTCCAATTAA 71 81 91 1	SAGATCCCT GAAGCTCACC AAAGGCACAG CAAGCCACTG GAGGTTAATT STCTAGGGA CTTCGAGTGG TTTCCGTGTC GTTCGGTGAC CTCCAATTAA  71 81 91 1	AGATCCCTGAAGCTCACCAAAGGCACAGCAAGCCACTGGAGGTTAATTTTGCCAAGGFTCTAGGGACTTCGAGTGGTTTCCGTGTCGTTCGGTGACCTCCAATTAAAACGGTTCCWN\$11111TGGAACTGA11111

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## SEQUENCE LISTING

Ala Ala Gly Val Leu Leu Leu Leu Leu Leu Ser Gly Gly Leu Gly Gly  5 10 15  gta cag gcg cag cgg ccg cag cag cag cag cgg cag tca cag gca cat cag Val Gln Ala Gln Arg Pro Gln Gln Gln Arg Gln Ser Gln Ala His Gln 20 25 30 35  caa aga ggt tta ttc cct gct gtc ctg aat ctt gct tct aat gct ctt Gln Arg Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser Asn Ala Leu 40 45 50  atc acg acc aat gca aca tgt gga gaa aaa gga cct gaa atg tac tgc Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys 55 60 65  aaa ttg gta gaa cat gtc cct ggg cag cct gtg agg aac ccg cag tgt Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys 70  cga atc tgc aat caa aac agc agc aat cca aac cag aga cac ccg att Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile 85 90 95																	
<pre>&lt;130&gt; 99,274-B1 &lt;140&gt; To Be Assigned &lt;141&gt; Filed Herewith &lt;160&gt; 32 &lt;170&gt; PatentIn Ver. 2.0 &lt;210&gt; 1</pre>	<11	0> Yu	rche	enco,	Pet	er											
<pre>&lt;140&gt; To Be Assigned &lt;141&gt; Filed Herewith </pre> <pre>&lt;160&gt; 32 </pre> <pre>&lt;170&gt; PatentIn Ver. 2.0 </pre> <pre>&lt;210 1</pre>	<120	0> La	mini	in 2	and	Meth	ods	For	Its	Use							
<pre>&lt;141&gt; Filed Herewith &lt;160&gt; 32 </pre> <pre>&lt;170&gt; PatentIn Ver. 2.0 </pre> <pre>&lt;210&gt; 1 &lt;211&gt; 9535 &lt;212&gt; DNA </pre> <pre>&lt;221&gt; CDS </pre> <pre>&lt;221&gt; CDS </pre> <pre>&lt;221&gt; Sig_peptide </pre> <pre>&lt;222&gt; (50)(115) </pre> <pre>&lt;400&gt; 1 cagcgactcc tctggctccc gagaagtgga tccggtcgcg gccactacg atg ccg gga 58</pre>	<13	0> 99	274	-B1													
<pre>&lt;170&gt; PatentIn Ver. 2.0  &lt;210&gt; 1  &lt;211&gt; 9535  &lt;212&gt; DNA  &lt;213&gt; Homo sapiens  &lt;220&gt;  &lt;221&gt; CDS  &lt;222&gt; (50)(9379)  &lt;220&gt; &lt;221&gt; sig_peptide  &lt;222&gt; (50)(115)  &lt;400&gt; 1  cagcgactcc tctggctccc gagaagtgga tccggtcgcg gccactacg atg ccg gga 58</pre>																	
<pre>&lt;210&gt; 1 &lt;211&gt; 9535 &lt;212&gt; DNA &lt;213&gt; Homo sapiens </pre> <pre>&lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (50)(9379) </pre> <pre>&lt;220&gt; &lt;221&gt; Sig_peptide &lt;222&gt; (50)(115) </pre> <pre>&lt;400&gt; 1</pre>	<16	0> 32	:														
<pre>&lt;211&gt; 9535 &lt;212&gt; DNA &lt;213&gt; Homo sapiens </pre> <pre>&lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (50)(9379) </pre> <pre>&lt;220&gt; &lt;221&gt; sig_peptide &lt;222&gt; (50)(115) </pre> <pre>&lt;400&gt; 1</pre>	<17	0> Pa	tent	:In \	ær.	2.0											
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Val Gln Ala Gln Arg Pro Gln Gln Gln Arg Gln Ser Gln Ala His Gln  20 25 30 35  caa aga ggt tta ttc cct gct gtc ctg aat ctt gct tct aat gct ctt Gln Arg Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser Asn Ala Leu  40 45 50  atc acg acc aat gca aca tgt gga gaa aaa gga cct gaa atg tac tgc Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys  55 60 65  aaa ttg gta gaa cat gtc cct ggg cag cct gtg agg aac ccg cag tgt Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys  70 75 80  cga atc tgc aat caa aac agc agc aat cca aac cag aga cac ccg att Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile  85 90 95  aca aat gct att gat gga aag aac act tgg tgg cag agt ccc agt att Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile		Ala					Leu					Gly					106
Gln Arg Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser Asn Ala Leu 40 45 50  atc acg acc aat gca aca tgt gga gaa aaa gga cct gaa atg tac tgc 250 Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys 65 65  aaa ttg gta gaa cat gtc cct ggg cag cct gtg agg aac ccg cag tgt Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys 70 75 80  cga atc tgc aat caa aac agc agc aat cca aac cag aga cac ccg att Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile 85 90 95  aca aat gct att gat gga aag aac act tgg tgg cag agt ccc agt att 394 Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile	Val					Pro					Gln					Gln	154
Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys  55 60 65  aaa ttg gta gaa cat gtc cct ggg cag cct gtg agg aac ccg cag tgt Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys  70 75 80  cga atc tgc aat caa aac agc agc aat cca aac cag aga cac ccg att Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile  85 90 95  aca aat gct att gat gga aag aac act tgg tgg cag agt ccc agt att Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile					Phe					Asn					Ala		202
Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys 70 75 80  cga atc tgc aat caa aac agc agc aat cca aac cag aga cac ccg att Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile 85 90 95  aca aat gct att gat gga aag aac act tgg tgg cag agt ccc agt att Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile				Asn					Glu					Met			250
Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile 85 90 95  aca aat gct att gat gga aag aac act tgg tgg cag agt ccc agt att 394 Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile	aaa Lys	ttg Leu	Val	gaa Glu	cat His	gtc Val	cct Pro	Gly	cag Gln	cct Pro	gtg Val	agg Arg	Asn	ccg Pro	cag Gln	tgt Cys	298
Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile	cga Arg	Ile	tgc Cys	aat Asn	caa Gln	aac Asn	Ser	agc Ser	aat Asn	cca Pro	aac Asn	Gln	aga Arg	cac Hís	ccg Pro	att Ile	346
	Thr	Asn	gct Ala	att Ile	gat Asp	Gly	aag Lys	aac Asn	act Thr	tgg Trp	Trp	cag Gln	agt Ser	ccc Pro	agt Ser	Ile	394

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			cag Gln 135													490
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	aac Asn															1258
	cca Pro 405															1306
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	ccc Pro 485															1546
	aaa Lys															1594
	gag Glu															1642
	acc Thr															1690
	cct Pro															1738
	cag Gln 565															1786
	agc Ser															1834
	gca Ala															1882

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Asn Asp Asn Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp Ser Leu Ser 870 875 880	2698
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		Cys Gln Gln		cct ctg att tct Pro Leu Ile Ser 1475	4474
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1820

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			aac gac aca Asn Asp Thr 2045		
Leu Ala Gln			aac ctc gat Asn Leu Asp		

aat tac aat aa Asn Tyr Asn Lys 2070	s Leu Ala Asp	age gte gee a Ser Val Ala 1 2075	aaa acg aat gct g Lys Thr Asn Ala V 2080	tg gtt 6298 al Val
		Ile Ile Ala	gat gca gat gcc a Asp Ala Asp Ala T 2095	
aaa aat tta gaa Lys Asn Leu Glu 2100	a cag gaa gct u Gln Glu Ala 2105	Asp Arg Leu	ata gat aaa ctc a Ile Asp Lys Leu L 110	aa ccc 6394 ys Pro 2115
			aac atc tct gag a Asn Ile Ser Glu I 21	
	n Gln Ala Arg		aat tot ato aaa g Asn Ser Ile Lys V 2145	
gtg tct tca ggs Val Ser Ser Gly 2150	y Gly Asp Cys	att cga aca t Ile Arg Thr 1 2155	tac aaa cca gaa a Tyr Lys Pro Glu I 2160	tc aag 6538 le Lys
			gta aag aca gct g Val Lys Thr Ala V 2175	
gat aac ctc ctc Asp Asn Leu Leu 2180	c ttt tat ctt u Phe Tyr Leu 2185	Gly Ser Ala 1	aaa ttt att gac t Lys Phe Ile Asp P 190	tt ctg 6634 The Leu 2195
			ttc ctc tgg gat g Phe Leu Trp Asp V 22	
	y Arg Val Glu		ttg act att gat g Leu Thr Ile Asp A 2225	
	g Ile Val Ala		ggg aga aat gga a Gly Arg Asn Gly T 2240	
tct gtg aga gcc Ser Val Arg Ala 2245		ccc aaa gcc a		gc aca 6826
	a Leu Asp Gly 2250	Pro Lys Ala s	age att gtg eec a Ser Ile Val Pro S 2255	
	2250 g tot oot coa	ggg tac acg a	Ser Ile Val Pro S	er Thr at gca 6874
His His Ser The 2260 aat gca atg cte	2250 g tct cct cca r Ser Pro Pro 2265	ggg tac acg a Gly Tyr Thr : 2: ggc ctg act s	Ser Ile Val Pro S 2255 att cta gat gtg g Ile Leu Asp Val A 270 ggg aaa tta aag a Gly Lys Leu Lys L	er Thr  at gca 6874 sp Ala 2275 ag gct 6922
His His Ser The 2260  aat gca atg ctg Asn Ala Met Lee	g tct cct cca r Ser Pro Pro 2265 g ttt gtt ggt u Phe Val Gly 2280 t gtg att aca g Val Ile Thr	ggg tac acg a Gly Tyr Thr 1 2: ggc ctg act a Gly Leu Thr 6 2285	Ser Ile Val Pro S 2255 att cta gat gtg g Ile Leu Asp Val A 270 ggg aaa tta aag a Gly Lys Leu Lys L	er Thr  at gca 6874 sp Ala 2275 ag gct 6922 ys Ala 90 ca tac 6970

Phe Asp A	Asn Lys 310	Pro Ile	Gly Leu 2315	Trp Asn		Glu Lys G 320	lu Gly	
gac tgc a Asp Cys I 2325	aaa gga Lys Gly	Cys Thr	gtc agt Val Ser 330	cct cag Pro Gln	gtg gaa ( Val Glu 2 2335	gat agt g Asp Ser G	ag ggg lu Gly	7066
act att o Thr Ile o 2340	caa ttt Gln Phe	gat gga Asp Gly 2345	gaa ggt Glu Gly	Tyr Ala	ttg gtc Leu Val :	agc cgt c Ser Arg F	rc att Pro Ile 2355	7114
cgc tgg t Arg Trp T	Tyr Pro					Phe Arg T		7162
tct tcg a Ser Ser S	agt gct Ser Ala 2375	ctt ctg Leu Leu	Met Tyr	ctt gcc Leu Ala 2380	aca cga ( Thr Arg	gac ctg a Asp Leu A 2385	iga gat irg Asp	7210
ttc atg a Phe Met S					Ile Lys			7258
ctg ggc t Leu Gly S 2405		Met Ala						7306
ggg aaa t Gly Lys 7 2420				Ser Arg				7354
ata tca a Ile Ser I	Ile Val	Asp Ile		Asn Gln		Asn Ile A		7402
	2	2440		2445		24	50	
tcg tct t Ser Ser S	tct gga	aac aac	Phe Gly	ctt gac		gca gat g	ac aaa	7450
ser ser s	tct gga Ser Gly 2455 ttt ggt	aac aac Asn Asn ggc ctg	Phe Gly	ctt gac Leu Asp 2460 ctg aga	aac ttg	gca gat g Ala Asp A 2465 agt atg a	gac aaa Asp Lys	7450 7498
ser ser s	tct gga Ser Gly 2455 ttt ggt Phe Gly 470 gaa gta	aac aac Asn Asn ggc ctg Gly Leu aat ctg Asn Leu	Phe Gly  cca acg Pro Thr  2475  aag aaa	ctt gac Leu Asp 2460 ctg aga Leu Arg	aac ttg Asn Leu 2	gca gat g Ala Asp F 2465  agt atg atg Ser Met I 480  ctc aaa g	gac aaa Asp Lys aaa gca Lys Ala	
ata tat tille Tyr I	tct gga Ser Gly 2455 ttt ggt Phe Gly 470 gaa gta Glu Val	aac aac Asn Asn ggc ctg Gly Leu aat ctg Asn Leu act ccg	Phe Gly  cca acg Pro Thr 2475  aag aaa Lys Lys 2490  tac aat	ctt gac Leu Asp 2460 ctg aga Leu Arg tat tcc Tyr Ser ata ctc	aac ttg Asn Leu 2 ggc tgc Gly Cys 2495 agt agt	gca gat c Ala Asp 7 2465  agt atg a Ser Met I 480  ctc aaa g Leu Lys 7	gac aaa usp Lys aaa gca uys Ala gat att usp Ile	7498
ata tat to the state of the sta	tct gga Ser Gly 2455 ttt ggt Phe Gly 470 gaa gta Glu Val tca aga Ser Arg acc aaa Thr Lys	aac aac Asn Asn  ggc ctg Gly Leu  aat ctg Asn Leu  act ccg Thr Pro 2505 gga tgt	Cca acg Pro Thr 2475 aag aaa Lys Lys 2490 tac aat Tyr Asn	ctt gac Leu Asp 2460  ctg aga Leu Arg  tat tcc Tyr Ser  ata ctc Ile Leu gag aat	aac ttg Asn Leu 2 ggc tgc Gly Cys 2495 agt agt Ser Ser 2510 gtt tac	gca gat g Ala Asp F 2465  agt atg atg Ser Met I 480  ctc aaa g Leu Lys F ccc gat t Pro Asp T aca gtt a	gac aaa gca ays Ala gat att asp Ile cat gtt Yal 2515	7498 7546
ata tat tile Tyr tile 24 agg cca garger compared to 2485 gaa att tile Clu Ile S 2500 ggt gtt a	tct gga Ser Gly 2455  ttt ggt Phe Gly 470  gaa gta Glu Val  tca aga Ser Arg  acc aaa Thr Lys cct ggt	aac aac Asn Asn  ggc ctg Gly Leu  aat ctg Asn Leu  act ccg Thr Pro 2505  gga tgt Gly Cys 2520  ttt gtg	Phe Gly  cca acg Pro Thr 2475  aag aaa Lys Lys 2490  tac aat Tyr Asn  tcc ctg Ser Leu  gag ctc Glu Leu	ctt gac Leu Asp 2460  ctg aga Leu Arg  tat tcc Tyr Ser  ata ctc Ile Leu  gag aat Glu Asn 2525	aac ttg Asn Leu 2 ggc tgc Gly Cys 2495 agt agt Ser Ser 2510 gtt tac Val Tyr	gca gat gat gat atg atg atg atg atg atg at	gac aaa gca ays Ala gat att asp Ile cat gtt 2515 agc ttt ser Phe 330 gta gga	7498 7546 7594

· ...

2560

101/0500/113/0

2555

2330	2555		2560	
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cag act gga cag Gln Thr Gly Gln 2580	gcc tat tat gta Ala Tyr Tyr Val 2585	ata ctc ctc Ile Leu Leu 2590	Asn Arg Gly Arg	ctg 7834 Leu 595
Glu Val His Leu	tcc aca ggg gca Ser Thr Gly Ala 2600	cga aca atg Arg Thr Met . 2605	agg aaa att gtc Arg Lys Ile Val 2610	atc 7882 Ile
	aat ctg ttt cat Asn Leu Phe His			
	aga ggc atc ttt Arg Gly Ile Phe 2635	Thr Val Gln		
	aac ctg aca gtt Asn Leu Thr Val 2650	Glu Gln Pro		
	ggt gct cca cct Gly Ala Pro Pro 2665		Pro Ser Pro Leu	
Asn Ile Pro Pro	ttt gaa ggc tgc Phe Glu Gly Cys 2680			
	ttt gca agg cct Phe Ala Arg Pro			
	cat cag aaa ctc His Gln Lys Leu 2715	Arg Glu Asp		
	gtt atc cag cct Val Ile Gln Pro 2730	Glu Pro Val		
	cca gtt ctg aca Pro Val Leu Thr 2745		Cys Ala Ala Glu	
Glu Pro Ala Leu	ttg ata ggg agc Leu Ile Gly Ser 2760			
	att gca ttt gat Ile Ala Phe Asp			
	gaa gta aga acc Glu Val Arg Thr 2795	Glu Ala Glu		

tac atg gct Tyr Met Ala 2805	Ala Ile Asn	cat gct gat His Ala Asp 2810	ttt gca aca Phe Ala Thr 2815	gtt cag ctg Val Gln Leu	aga 8506 Arg
aat gga ttg Asn Gly Leu 2820	ccc tac ttc Pro Tyr Phe 2825	agc tat gac Ser Tyr Asp	ttg ggg agt Leu Gly Ser 2830	ggg gac acc Gly Asp Thr	cac 8554 His !835
acc atg atc Thr Met Ile	ccc acc aaa Pro Thr Lys 2840	Ile Asn Asp	ggc cag tgg Gly Gln Trp 2845	cac aag att His Lys Ile 2850	aag 8602 Lys
Ile Met Arg	agt aag caa Ser Lys Gln 1855	gaa gga att Glu Gly Ile 2860	Leu Tyr Val	gat ggg gct Asp Gly Ala 2865	tcc 8650 Ser
aac aga acc Asn Arg Thr 2870	atc agt ccc Ile Ser Pro	aaa aaa gcc Lys Lys Ala 2875	Asp Ile Leu	gat gtc gtg Asp Val Val 2880	gga 8698 Gly
	Val Gly Gly			acc cga aga Thr Arg Arg	
				aat ctc cac Asn Leu His	
		Leu Glu Gln		age tte cat Ser Phe His 2930	
Gly Thr Cys				ttt gac gga Phe Asp Gly 2945	
			Lys Val Gly	ttg gac ctt Leu Asp Leu 2960	
	Glu Phe Ala			gtt ctt ctg Val Leu Leu	
				atg att gat Met Ile Asp 2	
		Asp Asn Gly		ttc act gct Phe Thr Ala 3010	
Tyr Asp Ala				caa tgg cat Gln Trp His 3025	
			Ile Glu Leu	aca gtc gat Thr Val Asp 3040	

Asn	cag Gln 3045	gtg Val	gaa Glu	gcc Ala	Gln	agc Ser 3050	cca Pro	aac Asn	cca Pro	Ala	tct Ser 3055	aca Thr	tca Ser	gct Ala	gac Asp	9226
aca Thr 3060	Asn	gac Asp	cct Pro	Val	ttt Phe 3065	gtt Val	gga Gly	ggc Gly	Phe	cca Pro 3070	gat Asp	gac Asp	ctc Leu	aag Lys	cag Gln 3075	9274
ttt Phe	ggc Gly	cta Leu	Thr	acc Thr 3080	agt Ser	att Ile	ccg Pro	Phe	cga Arg 3085	ggt Gly	tgc Cys	atc Ile	Arg	tcc Ser 3090	ctg Leu	9322
aag Lys	ctc Leu	Thr	aaa Lys 3095	ggc Gly	aca Thr	ggc Gly	Lys	cca Pro 3100	ctg Leu	gag Glu	gtt Val	Asn	ttt Phe 3105	gcc Ala	aag Lys	9370
	ctg Leu		ctga	9999	gog t	tcaa	accts	gt at	cato	gccca	a gco	aact	aat			9419
aaaa	ataa	gt g	gtaad	ccca	ag ga	agag	gtoto	g tca	aaaa	caag	tata	tcaa	agt a	aaaa	caaaca	9479
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<400		_														
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Leu	Gly	Gly	Val 20	Gln	Ala	Gln	Arg	Pro 25	Gln	Gln	Gln	Arg	Gln 30	Ser	Gln	
Ala	His	Gln 35	Gln	Arg	Gly	Leu	Phe 40	Pro	Ala	Val	Leu	Asn 45	Leu	Ala	Ser	
naA	Ala 50	Leu	Il.e	Thr	Thr	Asn 55	Ala	Thr	Cys	Gly	Glu 60	Lys	Gly	Pro	Glu	
Met 65	Tyr	Сув	Lys	Leu	Val 70	Glu	His	Val	Pro	Gly 75	Gln	Pro	Val	Arg	Asn 80	
Pro	Gln	Cys	Arg	Ile 85	Cys	Asn	Gln	Asn	Ser 90	Ser	Asn	Pro	Asn	Gln 95	Arg	
His	Pro	Ile	Thr 100	Asn	Ala	Ile	Asp	Gly 105	Lys	Asn	Thr	Trp	Trp 110	Gln	Ser	
Pro	Ser	Ile 115	Lys	Asn	Gly	Ile	Glu 120	Tyr	His	Tyr	Val	Thr 125	Ile	Thr	Leu	
Asp	Leu 130	Gln	Gln	Val	Phe	Gln 135	Ile	Ala	Tyr	Val	Ile 140	Val	Lys	Ala	Ala	
Asn 145	Ser	Pro	Arg	Pro	Gly 150	Asn	Trp	Ile	Leu	Glu 155	Arg	Ser	Leu	Asp	Asp 160	

Val Glu Tyr Lys Pro Trp Gln Tyr His Ala Val Thr Asp Thr Glu Cys Leu Thr Leu Tyr Asn Ile Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala 180 185 190 Lys Asp Asp Glu Val 11e Cys Thr Ser Phe Tyr Ser Lys Ile His Pro 195 200 205 Leu Glu Asn Gly Glu Ile His Ile Ser Leu Ile Asn Gly Arg Pro Ser 210 215 220 Ala Asp Asp Pro Ser Pro Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr Ile Arg Leu Arg Phe Gln Arg Ile Arg Thr Leu Asn Ala Asp Leu Met 250 Met Phe Ala His Lys Asp Pro Arg Glu Ile Asp Pro Ile Val Thr Arg 260 265 270. Arg Tyr Tyr Tyr Ser Val Lys Asp Ile Ser Val Gly Gly Met Cys Ile 275 280 285 Cys Tyr Gly His Ala Arg Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys 290 295 300 Ser Arg Cys Glu Cys Glu His Asn Thr Cys Gly Asp Ser Cys Asp Gln 305 310 315 320 Cys Cys Pro Gly Phe His Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu 325  $\phantom{-}330\phantom{+}\cdot\phantom{0}335$ Thr Lys Thr Glu Cys Glu Ala Cys Asn Cys His Gly Lys Ala Glu Glu 340 345 350Cys Tyr Tyr Asp Glu Asn Val Ala Arg Arg Asn Leu Ser Leu Asn Ile 355 360 365 Arg Gly Lys Tyr Ile Gly Gly Gly Val Cys Ile Asn Cys Thr Gln Asn 370 \$375\$Thr Ala Gly Ile Asn Cys Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro 385 390 395 400 Lys Gly Val Ser Pro Asn Tyr Pro Arg Pro Cys Gln Pro Cys His Cys Asp Pro Ile Gly Ser Leu Asn Glu Val Cys Val Lys Asp Glu Lys His 425 Ala Arg Arg Gly Leu Ala Pro Gly Ser Cys His Cys Lys Thr Gly Phe 435  $\phantom{\bigg|}440\phantom{\bigg|}$  445 Gly Gly Val Ser Cys Asp Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro 450 455 460 Asp Cys Lys Ala Cys Asn Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp Pro Cys Phe Gly Pro Cys Ile Cys Lys Glu Asn Val Glu Gly Gly Asp

				485					490					495	
Сув	Ser	Arg	Сув 500	Lys	Ser	Gly	Phe	Phe 505	Asn	Leu	Gln	Glu	Asp 510	Asn	Trp
Lys	Gly	Cys 515	Asp	Glu	Cys	Phe	Cys 520	Ser	Gly	Val	Ser	Asn 525	Arg	Cys	Gln
Ser	Ser 530	Tyr	Trp	Thr	Tyr	Gly 535	Lys	Ile	Gln	Asp	Met 540	Ser	Gly	Trp	Tyr
Leu 545	Thr	Asp	Leu	Pro	Gly 550	Arg	Ile	Arg	Val	Ala 555	Pro	Gln	Gln	Asp	Asp 560
Leu	Asp	Ser	Pro	Gln 565	Gln	Ile	Ser	Ile	Ser 570	Asn	Ala	Glu	Ala	Arg 575	Gln
Ala	Leu	Pro	His 580	Ser	Tyr	Tyr	Trp	Ser 585	Ala	Pro	Ala	Pro	Tyr 590	Leu	Gly
Asn	Lys	Leu 595	Pro	Ala	Val	Gly	Gly 600	Gln	Leu	Thr	Phe	Thr 605	Ile	Ser	Tyr
Asp	Leu 610	Glu	Glu	Glu	Glu	Glu 615	Asp	Thr	Glu	Arg	Val 620	Leu	Gln	Leu	Met
Ile 625	Ile	Leu	Glu	Gly	Asn 630	Asp	Leu	Ser	Ile	Ser 635	Thr	Ala	Gln	Asp	Glu 640
Val	Tyr	Leu	His	Pro 645	Ser	Glu	Glu	His	Thr 650	Asn	Val	Leu	Leu	Leu 655	Lys
Glu	Glu	Ser	Phe 660	Thr	Ile	His	Gly	Thr 665	His	Phe	Pro	Val	Arg 670	Arg	Lys
Glu	Phe	Met 675	Thr	Val	Leu	Ala	Asn 680	Leu	Lys	Arg	Val	Leu 685	Leu	Gln	Ile
Thr	Tyr 690	Ser	Phe	Gly	Met	Asp 695	Ala	Ile	Phe	Arg	Leu 700	Ser	Ser	Val	Asn
Leu 705	Glu	Ser	Ala	Val	Ser 710	Tyr	Pro	Thr	Asp	Gly 7 <b>1</b> 5	Ser	Ile	Ala	Ala	Ala 720
Val	Glu	Val	Суз	Gln 725	Сув	Pro	Pro	Gly	Tyr 730	Thr	Gly	Ser	Ser	Cys 735	Glu
Ser	Суз	Trp	Pro 740	Arg	His	Arg	Arg	Val 745	Asn	Gly	Thr	Ile	Phe 750	Gly	Gly
Ile	Cys	Glu 755	Pro	Cys	Gln	Сув	Phe 760	Gly	His	Ala	Glu	Ser 765	Сув	Asp	Asp
Val	Thr 770	Gly	Glu	Cys	Leu	<b>Asn</b> 775	Cys	Lys	Asp	His	Thr 780	Gly	Gly	Pro	Tyr
Сув 785	qaA	Lys	Суѕ	Leu	Pro 790	Gly	Phe	Tyr	Gly	Glu 795	Pro	Thr	Lys	Gly	Thr 800
Ser	Glu	Asp	Cys	Gln 805	Pro	Сув	Ala	Cys	Pro 810	Leu	Asn	Ile	Pro	Ser 815	Asn

Asn Phe Ser Pro Thr Cys His Leu Asp Arg Ser Leu Gly Leu Ile Cys 820 825 830

- Asp Gly Cys Pro Val Gly Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala 835 840 845
- Glu Gly Tyr Phe Gly Gln Pro Ser Val Pro Gly Gly Ser Cys Gln Pro 850 855 860
- Cys Gln Cys Asn Asp Asn Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp 865 870 880
- Ser Leu Ser Gly Ser Cys Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg 885 890 895
- Tyr Cys Glu Leu Cys Ala Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala 900 905 910
- Lys Asn Cys Gln Pro Cys Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu 915 920 925
- Val Cys His Ser Gln Thr Gly Gln Cys Glu Cys Arg Ala Asn Val Gln 930 935 940
- Gly Gln Arg Cys Asp Lys Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser 945 950 955 960
- Ala Arg Gly Cys Val Pro Cys Asn Cys Asn Ser Phe Gly Ser Lys Ser 965 970 970
- Phe Asp Cys Glu Glu Ser Gly Gln Cys Trp Cys Gln Pro Gly Val Thr 980 985 990
- Gly Lys Lys Cys Asp Arg Cys Ala His Gly Tyr Phe Asn Phe Gln Glu 995 1000 1005
- Gly Gly Cys Thr Ala Cys Glu Cys Ser His Leu Gly Asn Asn Cys Asp 1010 1015 1020
- Pro Lys Thr Gly Arg Cys Ile Cys Pro Pro Asn Thr Ile Gly Glu Lys 025 1030 1035
- Cys Ser Lys Cys Ala Pro Asn Thr Trp Gly His Ser Ile Thr Thr Gly 1045 1050 1055
- Cys Lys Ala Cys Asn Cys Ser Thr Val Gly Ser Leu Asp Phe Gln Cys 1060 1065 1070
- Asn Val Asn Thr Gly Gln Cys Asn Cys His Pro Lys Phe Ser Gly Ala 1075 1080 1085
- Lys Cys Thr Glu Cys Ser Arg Gly His Trp Asn Tyr Pro Arg Cys Asn 1090 1095 1100
- Leu Cys Asp Cys Phe Leu Pro Gly Thr Asp Ala Thr Thr Cys Asp Ser 105 1110 1115 1120
- Glu Thr Lys Lys Cys Ser Cys Ser Asp Gln Thr Gly Gln Cys Thr Cys 1125 1130 1135

Lys Val Asn Val Glu Gly Ile His Cys Asp Arg Cys Arg Pro Gly Lys 1140 1145 1150

- Phe Gly Leu Asp Ala Lys Asn Pro Leu Gly Cys Ser Ser Cys Tyr Cys 1155 1160 1165
- Phe Gly Thr Thr Thr Gln Cys Ser Glu Ala Lys Gly Leu Ile Arg Thr 1170 1175 1180
- Trp Val Thr Leu Lys Ala Glu Gln Thr IIe Leu Pro Leu Val Asp Glu 185 1190 1195 1200
- Ala Leu Gln His Thr Thr Thr Lys Gly Ile Val Phe Gln His Pro Glu 1205 1210 1215
- Ile Val Ala His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro 1220 1225 1230
- Phe Tyr Trp Lys Leu Pro Glu Gln Phe Glu Gly Lys Lys Leu Met Ala 1235 1240 1245
- Tyr Gly Gly Lys Leu Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu 1250 1255 1260
- Thr Gly Phe Ser Thr Tyr Asn Pro Gln Val Ile Ile Arg Gly Gly Thr 265 1270 1275 1280
- Pro Thr His Ala Arg Ile Ile Val Arg His Met Ala Ala Pro Leu Ile 1285 1290 1295
- Gly Gln Leu Thr Arg His Glu Ile Glu Met Thr Glu Lys Glu Trp Lys 1300 1305 1310
- Tyr Tyr Gly Asp Asp Pro Arg Val His Arg Thr Val Thr Arg Glu Asp 1315 1320 1325
- Phe Leu Asp Ile Leu Tyr Asp Ile His Tyr Ile Leu Ile Lys Ala Thr 1330 1335 1340
- Tyr Gly Asn Phe Met Arg Gln Ser Arg Ile Ser Glu Ile Ser Met Glu 345 1350 1355 1360
- Val Ala Glu Gln Gly Arg Gly Thr Thr Met Thr Pro Pro Ala Asp Leu 1365 1370 1375
- Ile Glu Lys Cys Asp Cys Pro Leu Gly Tyr Ser Gly Leu Ser Cys Glu 1380 1385 1390
- Ala Cys Leu Pro Gly Phe Tyr Arg Leu Arg Ser Gln Pro Gly Gly Arg 1395 1400 1405
- Thr Pro Gly Pro Thr Leu Gly Thr Cys Val Pro Cys Gln Cys Asn Gly 1410 1415 1420
- His Ser Ser Leu Cys Asp Pro Glu Thr Ser Ile Cys Gln Asn Cys Gln 425 1430 1435 1440
- His His Thr Ala Gly Asp Phe Cys Glu Arg Cys Ala Leu Gly Tyr Tyr 1445 1450 1450 1455
- Gly Ile Val Lys Gly Leu Pro Asn Asp Cys Gln Gln Cys Ala Cys Pro

Leu Ile Ser Ser Ser Asn Asn Phe Ser Pro Ser Cys Val Ala Glu Gly 1480

1465

- Leu Asp Asp Tyr Arg Cys Thr Ala Cys Pro Arg Gly Tyr Glu Gly Gln
- Tyr Cys Glu Arg Cys Ala Pro Gly Tyr Thr Gly Ser Pro Gly Asn Pro
- Gly Gly Ser Cys Gln Glu Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro 1530
- Val Pro Cys Asp Pro Val Thr Gly Phe Cys Thr Cys Arg Pro Gly Ala 1545
- Thr Gly Arg Lys Cys Asp Gly Cys Lys His Trp His Ala Arg Glu Gly 1560
- Trp Glu Cys Val Phe Cys Gly Asp Glu Cys Thr Gly Leu Leu Gly 1575
- Asp Leu Ala Arg Leu Glu Gln Met Val Met Ser Ile Asn Leu Thr Gly 1590 1595
- Pro Leu Pro Ala Pro Tyr Lys Met Leu Tyr Gly Leu Glu Asn Met Thr
- Gln Glu Leu Lys His Leu Leu Ser Pro Gln Arg Ala Pro Glu Arg Leu 1625
- Ile Gln Leu Ala Glu Gly Asn Leu Asn Thr Leu Val Thr Glu Met Asn 1640
- Glu Leu Leu Thr Arg Ala Thr Lys Val Thr Ala Asp Gly Glu Gln Thr
- Gly Gln Asp Ala Glu Arg Thr Asn Thr Arg Ala Lys Ser Leu Gly Glu
- Phe Ile Lys Glu Leu Ala Arg Asp Ala Glu Ala Val Asn Glu Lys Ala
- Ile Lys Leu Asn Glu Thr Leu Gly Thr Arg Asp Glu Ala Phe Glu Arg 1705
- Asn Leu Glu Gly Leu Gln Lys Glu Ile Asp Gln Met Ile Lys Glu Leu 1720
- Arg Arg Lys Asn Leu Glu Thr Gln Lys Glu Ile Ala Glu Asp Glu Leu 1735
- Val Ala Ala Glu Ala Leu Leu Lys Lys Val Lys Lys Leu Phe Gly Glu 1750 1755
- Ser Arg Gly Glu Asn Glu Glu Met Glu Lys Asp Leu Arg Glu Lys Leu 1770
- Ala Asp Tyr Lys Asn Lys Val Asp Asp Ala Trp Asp Leu Leu Arg Glu 1785

Ala Thr Asp Lys Ile Arg Glu Ala Asn Arg Leu Phe Ala Val Asn Gln 1795 1800 1805

- Lys Asn Met Thr Ala Leu Glu Lys Lys Glu Ala Val Glu Ser Gly 1810 1815 1820
- Lys Arg Gln Ile Glu Asn Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp 825 1830 1835
- Glu Ala Asn Arg Leu Ala Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val 1845 1850 1855
- Glu Asp Ile Gln Thr Lys Leu Pro Pro Met Ser Glu Glu Leu Asn Asp 1860 1865 1870
- Lys Ile Asp Asp Leu Ser Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu 1875 1880 1885
- Lys Val Ser Gln Ala Glu Ser His Ala Ala Gln Leu Asn Asp Ser Ser 1890 1895 1900
- Ala Val Leu Asp Gly Ile Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn 905 1910 1915 1920
- Ala Thr Ala Ala Phe Lys Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp 1925 1930 1935
- Glu Ala Glu Lys Val Ala Lys Glu Ala Lys Asp Leu Ala His Glu Ala 1940 1945 1950
- Thr Lys Leu Ala Thr Gly Pro Arg Gly Leu Leu Lys Glu Asp Ala Lys 1955 1960 1965
- Gly Cys Leu Gln Lys Ser Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu 1970 1975 1980
- Ala Asn Asp Val Lys Glu Asn Glu Asp His Leu Asn Gly Leu Lys Thr 985 1990 1995 2000
- Arg Ile Glu Asn Ala Asp Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu 2005 2010 2015
- Asn Asp Thr Leu Gly Lys Leu Ser Ala Ile Pro Asn Asp Thr Ala Ala 2020 2025 2030
- Lys Leu Gln Ala Val Lys Asp Lys Ala Arg Gln Ala Asn Asp Thr Ala 2035 2040 2045
- Lys Asp Val Leu Ala Gln Ile Thr Glu Leu His Gln Asn Leu Asp Gly 2050 2055 2060
- Leu Lys Lys Asn Tyr Asn Lys Leu Ala Asp Ser Val Ala Lys Thr Asn 065 2070 2075 2080
- Ala Val Val Lys Asp Pro Ser Lys Asn Lys Ile Ile Ala Asp Ala Asp 2085 2090 2095
- Ala Thr Val Lys Asn Leu Glu Glu Glu Ala Asp Arg Leu Ile Asp Lys 2100 2105 2110

Leu Lys Pro Ile Lys Glu Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser 2115 2120 2125

- Glu Ile Lys Glu Leu Ile Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile 2130 2135 2140
- Lys Val Ser Val Ser Ser Gly Gly Asp Cys Ile Arg Thr Tyr Lys Pro 145 2150 2155 2160
- Glu Ile Lys Lys Gly Ser Tyr Asn Asn Ile Val Val Asn Val Lys Thr 2165 2170 2175
- Ala Val Ala Asp Asn Leu Leu Phe Tyr Leu Gly Ser Ala Lys Phe Ile 2180 · 2185 2190
- Asp Phe Leu Ala Ile Glu Met Arg Lys Gly Lys Val Ser Phe Leu Trp 2195 2200 2205
- Asp Val Gly Ser Gly Val Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile 2210 2215 2220
- Asp Asp Ser Tyr Trp Tyr Arg Ile Val Ala Ser Arg Thr Gly Arg Asn 225 2230 2235 2240
- Gly Thr Ile Ser Val Arg Ala Leu Asp Gly Pro Lys Ala Ser Ile Val 2245 2250 2255
- Pro Ser Thr His His Ser Thr Ser Pro Pro Gly Tyr Thr Ile Leu Asp \$2260\$ \$2265\$ \$2270
- Val Asp Ala Asn Ala Met Leu Phe Val Gly Gly Leu Thr Gly Lys Leu 2275 2280 2285
- Lys Lys Ala Asp Ala Val Arg Val Ile Thr Phe Thr Gly Cys Met Gly 2290 2295 2300
- Glu Thr Tyr Phe Asp Asn Lys Pro Ile Gly Leu Trp Asn Phe Arg Glu 305 2310 2315 2320
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- Ser Glu Gly Thr Ile Gln Phe Asp Gly Glu Gly Tyr Ala Leu Val Ser 2340 2345 2350
- Arg Pro Ile Arg Trp Tyr Pro Asn Ile Ser Thr Val Met Phe Lys Phe 2355 2360 2365
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- Ser Tyr Asp Leu Gly Ser Gly Met Ala Ser Val Val Ser Asn Gln Asn 2405 2410 2415
- His Asn Asp Gly Lys Trp Lys Ser Phe Thr Leu Ser Arg Ile Gln Lys 2420 2425 2430
- Gln Ala Asn Ile Ser Ile Val Asp Ile Asp Thr Asn Gln Glu Glu Asn

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2440

- Asp Asp Lys Ile Tyr Phe Gly Gly Leu Pro Thr Leu Arg Asn Leu Ser 465 2470 2475 2480
- Met Lys Ala Arg Pro Glu Val Asn Leu Lys Lys Tyr Ser Gly Cys Leu 2485 2490 2495
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- Lys Arg Arg Gln Thr Gly Gln Ala Tyr Tyr Val Ile Leu Leu Asn Arg 2580 2585 2590
- Gly Arg Leu Glu Val His Leu Ser Thr Gly Ala Arg Thr Met Arg Lys 2595 2600 2605
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- Gly Ala Ala Pro Ala Glu Ile Val Ile Gln Pro Glu Pro Val Pro Thr 2725 2730 2735
- Pro Ala Phe Pro Thr Pro Thr Pro Val Leu Thr His Gly Pro Cys Ala 2740 2745 2750
- Ala Glu Ser Glu Pro Ala Leu Leu Ile Gly Ser Lys Gln Phe Gly Leu 2755 2760 2765 .

Ser Arg Asn Ser His Ile Ala Ile Ala Phe Asp Asp Thr Lys Val Lys 2770 2780

- Asn Arg Leu Thr Ile Glu Leu Glu Val Arg Thr Glu Ala Glu Ser Gly 785 2790 2795 2800
- Leu Leu Phe Tyr Mct Ala Ala Ile Asn His Ala Asp Phe Ala Thr Val 2805 2810 2815
- Gln Leu Arg Asn Gly Leu Pro Tyr Phe Ser Tyr Asp Leu Gly Ser Gly 2820 2825 2830
- Asp Thr His Thr Met Ile Pro Thr Lys Ile Asn Asp Gly Gln Trp His 2835 2840 2845
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- Thr Ala Val Tyr Asp Ala Gly Val Pro Gly His Leu Cys Asp Gly Gln 3010 3015 3020
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- Val Asp Gly Asn Gln Val Glu Ala Gln Ser Pro Asn Pro Ala Ser Thr 3045 3050 3055
- Ser Ala Asp Thr Asn Asp Pro Val Phe Val Gly Gly Phe Pro Asp Asp 3060 3065 3070
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Leu Phe Pro Ala Val Leu Asn Leu Ala Ser Asn Ala Leu Ile Thr Thr
20 25 30

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Ile Glu Tyr His Tyr Val Thr Ile Thr Leu Asp Leu Gln Gln Val Phe
100 105 110

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Gln Tyr His Ala Val Thr Asp Thr Glu Cys Leu Thr Leu Tyr Asn Ile
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tac tgg agc							
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27

2736

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acc aag ggc at Thr Lys Gly II 1185	tt gtt ttt le Val Phe 1190	caa cat cca Gln His Pro	gag att gtt Glu Ile Val 1195	gcc cac atg ga Ala His Met As 120	p
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acg tct cct cca Thr Ser Pro Pro 2				
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cgt gtg att aca Arg Val Ile Thr 2275		s Met Gly Glu		
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ccc aac atc tcc Pro Asn Ile Ser 2340				
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Val 2	Glu 2370	Leu	Thr	Asp		His 2375	Ile	Lys	Val		Tyr 2380	Asp	Leu	Gly	Ser	
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			Tyr					Ser			tat Tyr		Gly			7488
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	Phe					Pro					gta Val					7584
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			Tyr					Asn			cgt Arg		Glu			7728
		Thr					Met				gtc Val	Ile				7776
	Asn					Gly					gtt Val 2					7824
act Thr	aga Arg	ggc Gly	atc Ile	ttt Phe	aca Thr	gtt Val	caa Gln	gtg Val	gat Asp	gaa Glu	aac Asn	aga Arg	aga Arg	tac Tyr	atg Met	7872

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acc cca gtt ctg Thr Pro Val Leu			la Glu Ser Glu	
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ccc acc aaa atc Pro Thr Lys Ile 2820				
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		Val	gac Asp 2980				Gly					Val				8976
	Val		gly ggg			Сув					His					9024
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Lys Asp Ile Ser Val Gly Gly Met Cys Ile Cys Tyr Gly His Ala Arg

Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys Ser Arg Cys Glu Cys Glu His Asn Thr Cys Gly Asp Ser Cys Asp Gln Cys Cys Pro Gly Phe His Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu Thr Lys Thr Glu Cys Glu 305 310 315 320 Ala Cys Asn Cys His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp Glu Asn 325 330 335Val Ala Arg Arg Asn Leu Ser Leu Asn Ile Arg Gly Lys Tyr Ile Gly Gly Gly Val Cys Ile Asn Cys Thr Gln Asn Thr Ala Gly Ile Asn Cys 360 Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro Lys Gly Val Ser Pro Asn 370  $\phantom{\bigg|}375\phantom{\bigg|}$  380  $\phantom{\bigg|}$  . Tyr Pro Arg Pro Cys Gln Pro Cys His Cys Asp Pro Ile Gly Ser Leu 385 390 395 400 Asn Glu Val Cys Val Lys Asp Glu Lys His Ala Arg Arg Gly Leu Ala Pro Gly Ser Cys His Cys Lys Thr Gly Phe Gly Gly Val Ser Cys Asp 420 425 430 Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro Asp Cys Lys Ala Cys Asn 435 440 445 Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp Pro Cys Phe Gly Pro Cys 450 455 460 Ile Cys Lys Glu Asn Val Glu Gly Gly Asp Cys Ser Arg Cys Lys Ser 465 470 475 480 Gly Phe Phe Asn Leu Gln Glu Asp Asn Trp Lys Gly Cys Asp Glu Cys 485 485 490 495 Phe Cys Ser Gly Val Ser Asn Arg Cys Gln Ser Ser Tyr Trp Thr Tyr 500 505 510 Gly Lys Ile Gln Asp Met Ser Gly Trp Tyr Leu Thr Asp Leu Pro Gly 515 520 525Arg Ile Arg Val Ala Pro Gln Gln Asp Asp Leu Asp Ser Pro Gln Gln Ile Ser Ile Ser Asn Ala Glu Ala Arg Gln Ala Leu Pro His Ser Tyr 545 550 555 560 Tyr Trp Ser Ala Pro Ala Pro Tyr Leu Gly Asn Lys Leu Pro Ala Val 565 570 575 Gly Gly Gln Leu Thr Phe Thr Ile Ser Tyr Asp Leu Glu Glu Glu 585 Glu Asp Thr Glu Arg Val Leu Gln Leu Met Ile Ile Leu Glu Gly Asn

595 600 605

Asp Leu Ser Ile Ser Thr Ala Gln Asp Glu Val Tyr Leu His Pro Ser 610 615 620

Glu Glu His Thr Asn Val Leu Leu Leu Lys Glu Glu Ser Phe Thr Ile 625 630 635 640

His Gly Thr His Phe Pro Val Arg Arg Lys Glu Phe Met Thr Val Leu 645 650 655

Ala Asn Leu Lys Arg Val Leu Leu Gln Ile Thr Tyr Ser Phe Gly Met 660 665 670

Asp Ala Ile Phe Arg Leu Ser Ser Val Asn Leu Glu Ser Ala Val Ser 675 680 685

Tyr Pro Thr Asp Gly Ser Ile Ala Ala Ala Val Glu Val Cys Gln Cys

Pro Pro Gly Tyr Thr Gly Ser Ser Cys Glu Ser Cys Trp Pro Arg His 705 710 715 720

Arg Arg Val Asn Gly Thr Ile Phe Gly Gly Ile Cys Glu Pro Cys Gln 725  $\phantom{\bigg|}730\phantom{\bigg|}735\phantom{\bigg|}$ 

Cys Phe Gly His Ala Glu Ser Cys Asp Asp Val Thr Gly Glu Cys Leu 740 745 750

Asn Cys Lys Asp His Thr Gly Gly Pro Tyr Cys Asp Lys Cys Leu Pro 755 760 765

Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr Ser Glu Asp Cys Gln Pro 770 780

Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn Asn Phe Ser Pro Thr Cys 785 790 795 800

His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Gly Cys Pro Val Gly 805 810 815

Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe Gly Gln 820 825 830

Pro Ser Val Pro Gly Gly Ser Cys Gln Pro Cys Gln Cys Asn Asp Asn 835 840 845

Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp Ser Leu Ser Gly Ser Cys 850 850

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Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala Lys Asn Cys Gln Pro Cys 885 890 895

Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu Val Cys His Ser Gln Thr 900 905 910

Gly Gln Cys Glu Cys Arg Ala Asn Val Gln Gly Gln Arg Cys Asp Lys 915 920 925

Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser Ala Arg Gly Cys Val Pro 930 935 940

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- Gly Gln Cys Trp Cys Gln Pro Gly Val Thr Gly Lys Lys Cys Asp Arg 965 970 975
- Cys Ala His Gly Tyr Phe Asn Phe Gln Glu Gly Gly Cys Thr Ala Cys 980 985 990
- Glu Cys Ser His Leu Gly Asn Asn Cys Asp Pro Lys Thr Gly Arg Cys 995 1000 1005
- Ile Cys Pro Pro Asn Thr Ile Gly Glu Lys Cys Ser Lys Cys Ala Pro 1010 1015 1020
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- Cys Asn Cys His Pro Lys Phe Ser Gly Ala Lys Cys Thr Glu Cys Ser 1060 1065 1070
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- Cys Ser Glu Ala Lys Gly Leu Ile Arg Thr Trp Val Thr Leu Lys Ala 1155 \$1160\$
- Glu Gln Thr Ile Leu Pro Leu Val Asp Glu Ala Leu Gln His Thr Thr 1170 1175 1180
- Thr Lys Gly Ile Val Phe Gln His Pro Glu Ile Val Ala His Met Asp 1185 1190 1195 1200
- Leu Met Arg Glu Asp Leu His Leu Glu Pro Phe Tyr Trp Lys Leu Pro 1205 1210 · 1215
- Glu Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly Lys Leu Lys 1220 1225 1230
- Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu Thr Gly Phe Ser Thr Tyr 1235 1240 1245

Asn Pro Gln Val Ile Ile Arg Gly Gly Thr Pro Thr His Ala Arg Ile 1250 1255 1260

- Ile Val Arg His Met Ala Ala Pro Leu Ile Gly Gln Leu Thr Arg His 1265 1270 1275 1280
- Glu fle Glu Met Thr Glu Lys Glu Trp Lys Tyr Tyr Gly Asp Asp Pro 1285 1290 1295
- Arg Val His Arg Thr Val Thr Arg Glu Asp Phe Leu Asp Ile Leu Tyr 1300 1305 1310
- Asp Ile His Tyr Ile Leu Ile Lys Ala Thr Tyr Gly Asn Phe Met Arg 1315 1320 1325
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- Gly Thr Thr Met Thr Pro Pro Ala Asp Leu Ile Glu Lys Cys Asp Cys 1345 1350 1355 1360
- Pro Leu Gly Tyr Ser Gly Leu Ser Cys Glu Ala Cys Leu Pro Gly Phe 1365 1370 1375
- Tyr Arg Leu Arg Ser Gln Pro Gly Gly Arg Thr Pro Gly Pro Thr Leu 1380 1385 1390
- Gly Thr Cys Val Pro Cys Gln Cys Asn Gly His Ser Ser Leu Cys Asp 1395 1400 1405
- Pro Glu Thr Ser Ile Cys Gln Asn Cys Gln His His Thr Ala Gly Asp 1410 1415 1420
- Phe Cys Glu Arg Cys Ala Leu Gly Tyr Tyr Gly Ile Val Lys Gly Leu 1425 1430 1435 1440
- Pro Asn Asp Cys Gln Gln Cys Ala Cys Pro Leu Ile Ser Ser Ser Asn 1445 1450 1455
- Asn Phe Ser Pro Ser Cys Val Ala Glu Gly Leu Asp Asp Tyr Arg Cys 1460 1465 1470
- Thr Ala Cys Pro Arg Gly Tyr Glu Gly Gln Tyr Cys Glu Arg Cys Ala 1475 1480 1485
- Pro Gly Tyr Thr Gly Ser Pro Gly Asn Pro Gly Gly Ser Cys Gln Glu 1490 1495 1500
- Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro Val Pro Cys Asp Pro Val 1505 1510 1515 1520
- Thr Gly Phe Cys Thr Cys Arg Pro Gly Ala Thr Gly Arg Lys Cys Asp 1525 1530 1535
- Gly Cys Lys His Trp His Ala Arg Glu Gly Trp Glu Cys Val Phe Cys 1540 1545 1550
- Gly Asp Glu Cys Thr Gly Leu Leu Gly Asp Leu Ala Arg Leu Glu 1555 1560 1565
- Gln Met Val Met Ser Ile Asn Leu Thr Gly Pro Leu Pro Ala Pro Tyr

1570 1575 1580

Lys Met Leu Tyr Gly Leu Glu Asn Met Thr Gln Glu Leu Lys His Leu 1585 1590 1595 1600

- Leu Ser Pro Gln Arg Ala Pro Glu Arg Leu Ile Gln Leu Ala Glu Gly
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- Thr Lys Val Thr Ala Asp Gly Glu Gln Thr Gly Gln Asp Ala Glu Arg 1635 1640 1645
- Thr Asn Thr Arg Ala Lys Ser Leu Gly Glu Phe Ile Lys Glu Leu Ala 1650 1655 1660
- Arg Asp Ala Glu Ala Val Asn Glu Lys Ala Ile Lys Leu Asn Glu Thr 1665 1670 1680
- Leu Gly Thr Arg Asp Glu Ala Phe Glu Arg Asn Leu Glu Cly Leu Gln 1685 1690 1695
- Lys Glu Ile Asp Gln Met Ile Lys Glu Leu Arg Arg Lys Asn Leu Glu 1700 1705 1710
- Thr Gln Lys Glu Ile Ala Glu Asp Glu Leu Val Ala Ala Glu Ala Leu 1715 1720 1725
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- Glu Met Glu Lys Asp Leu Arg Glu Lys Leu Ala Asp Tyr Lys Asn Lys 1745 1750 1755 1760
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- Glu Ala Asn Arg Leu Phe Ala Val Asn Gln Lys Asn Met Thr Ala Leu 1780 1785 1790
- Glu Lys Lys Glu Ala Val Glu Ser Gly Lys Arg Gln Ile Glu Asn 1795 1800 1805
- Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp Glu Ala Asn Arg Leu Ala 1810 1815 1820
- Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val Glu Asp Ile Gln Thr Lys 1825 1830 1835 1840
- Leu Pro Pro Met Ser Glu Glu Leu Asn Asp Lys Ile Asp Asp Leu Ser 1845 1850 1855
- Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu Lys Val Ser Gln Ala Glu 1860 1865 1870
- Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu Asp Gly Ile 1875 1880 1885
- Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala Phe Lys 1890 1895 1900

Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys Val Ala 1905 1910 1915 1920

- Lys Glu Ala Lys Asp Leu Ala His Glu Ala Thr Lys Leu Ala Thr Gly 1925 1930 1935
- Pro Arg Gly Leu Leu Lys Glu Asp Ala Lys Gly Cys Leu Gln Lys Ser 1940 1945 1950
- Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu Ala Asn Asp Val Lys Glu 1955 1960 1965
- Asn Glu Asp His Leu Asn Gly Leu Lys Thr Arg Ile Glu Asn Ala Asp 1970 1975 1980
- Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu Asn Asp Thr Leu Gly Lys 1985 1990 1995 2000
- Leu Ser Ala Ile Pro Asn Asp Thr Ala Ala Lys Leu Gln Ala Val Lys 2005 2010 2015
- Asp Lys Ala Arg Gln Ala Asn Asp Thr Ala Lys Asp Val Leu Ala Gln 2020 2025 2030
- Ile Thr Glu Leu His Gln Asn Leu Asp Gly Leu Lys Lys Asn Tyr Asn 2035 2040 2045
- Lys Leu Ala Asp Ser Val Ala Lys Thr Asn Ala Val Val Lys Asp Pro 2050 2055 2060
- Ser Lys Asn Lys Ile Ile Ala Asp Ala Asp Ala Thr Val Lys Asn Leu 2065 2070 2075 2080
- Glu Gln Glu Ala Asp Arg Leu Ile Asp Lys Leu Lys Pro Ile Lys Glu 2085 2090 2095
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- Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile Lys Val Ser Val Ser Ser 2115 2120 2125
- Gly Gly Asp Cys Ile Arg Thr Tyr Lys Pro Glu Ile Lys Lys Gly Ser 2130 2135 2140
- Tyr Asn Asn Ile Val Val Asn Val Lys Thr Ala Val Ala Asp Asn Leu 2145 2150 2155 2160
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- Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile Asp Asp Ser Tyr Trp Tyr 2195 2200 2205
- Arg Ile Val Ala Ser Arg Thr Gly Arg Asn Gly Thr Ile Ser Val Arg 2210 2215 2220

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- Thr Ser Pro Pro Gly Tyr Thr Ile Leu Asp Val Asp Ala Asn Ala Met 2245 2250 2255
- Leu Phe Val Gly Gly Leu Thr Gly Lys Leu Lys Lys Ala Asp Ala Val 2260 2265 2270
- Arg Val Ile Thr Phe Thr Gly Cys Met Gly Glu Thr Tyr Phe Asp Asn 2275 2280 2285
- Lys Pro Ile Gly Leu Trp Asn Phe Arg Glu Lys Glu Gly Asp Cys Lys 2290 2295 2300
- Gly Cys Thr Val Ser Pro Gln Val Glu Asp Ser Glu Gly Thr Ile Gln 2305 2310 2315 2320
- Phe Asp Gly Glu Gly Tyr Ala Leu Val Ser Arg Pro Ile Arg Trp Tyr 2325 2330 2335
- Pro Asn Ile Ser Thr Val Met Phe Lys Phe Arg Thr Phe Ser Ser Ser 2340 2345 2350
- Ala Leu Leu Met Tyr Leu Ala Thr Arg Asp Leu Arg Asp Phe Met Ser 2355 2360 2365
- Val Glu Leu Thr Asp Gly His Ile Lys Val Ser Tyr Asp Leu Gly Ser 2370 2375 2380
- Gly Met Ala Ser Val Val Ser Asn Gln Asn His Asn Asp Gly Lys Trp 2385 2390 2395 2400
- Lys Ser Phe Thr Leu Ser Arg Ile Gln Lys Gln Ala Asn Ile Ser Ile 2405 2410 2415
- Val Asp Ile Asp Thr Asn Glu Glu Glu Asn Ile Ala Thr Ser Ser Ser 2420 2425 2430
- Gly Asn Asn Phe Gly Leu Asp Leu Lys Ala Asp Asp Lys Ile Tyr Phe 2435 2440 2445
- Gly Gly Leu Pro Thr Leu Arg Asn Leu Ser Met Lys Ala Arg Pro Glu 2450 2455 2460
- Val Asn Leu Lys Lys Tyr Ser Gly Cys Leu Lys Asp Ile Glu Ile Ser 2465 2470 2475 2480
- Arg Thr Pro Tyr Asn Ile Leu Ser Ser Pro Asp Tyr Val Gly Val Thr \$2485\$ \$2490\$
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- Ala His Gln Lys Leu Arg Glu Asp Glu Asp Gly Ala Ala Pro Ala Glu 2690 2695 2700
- Ile Val Ile Gln Pro Glu Pro Val Pro Thr Pro Ala Phe Pro Thr Pro 2705 2710 2715 2720
- Thr Pro Val Leu Thr His Gly Pro Cys Ala Ala Glu Ser Glu Pro Ala 2725 2730 2735 .
- Leu Leu Ile Gly Ser Lys Gln Phe Gly Leu Ser Arg Asn Ser His Ile 2740 2750
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- Pro Thr Lys Ile Asn Asp Gly Gln Trp His Lys Ile Lys Ile Met Arg 2820 2825 2830
- Ser Lys Gln Glu Gly Ile Leu Tyr Val Asp Gly Ala Ser Asn Arg Thr 2835 2840 2845
- Ile Ser Pro Lys Lys Ala Asp Ile Leu Asp Val Val Gly Met Leu Tyr 2850 2856
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Thr Tyr Ser Ile Asp Gly Cys Val Arg Asn Leu His Met Ala Glu Ala 2885 2890 Pro Ala Asp Leu Glu Gln Pro Thr Ser Ser Phe His Val Gly Thr Cys 2900 Phe Ala Asn Ala Gin Arg Gly Thr Tyr Phe Asp Gly Thr Gly Phe Ala Lys Ala Val Gly Gly Phe Lys Val Gly Leu Asp Leu Leu Val Glu Phe 2935 Glu Phe Ala Thr Thr Thr Thr Gly Val Leu Leu Gly Ile Ser Ser Gln Lys Met Asp Gly Met Gly Ile Glu Met Ile Asp Glu Lys Leu Met 2970 Phe His Val Asp Asn Gly Ala Gly Arg Phe Thr Ala Val Tyr Asp Ala 2980 2985 2990 Gly Val Pro Gly His Leu Cys Asp Gly Gln Trp His Lys Val Thr Ala 3000 Asn Lys Ile Lys His Arg Ile Glu Leu Thr Val Asp Gly Asn Gln Val 3015 Glu Ala Gln Ser Pro Asn Pro Ala Ser Thr Ser Ala Asp Thr Asn Asp 3025 3030 3035 Pro Val Phe Val Gly Gly Phe Pro Asp Asp Leu Lys Gln Phe Gly Leu 3045 3050 Thr Thr Ser Ile Pro Phe Arg Gly Cys Ile Arg Ser Leu Lys Leu Thr Lys Gly Thr Gly Lys Pro Leu Glu Val Asn Phe Ala Lys Ala Leu Glu 3080 Leu <210> 5 <211> 9534 <212> DNA <213> Homo sapiens <221> CDS <222> (50)..(9379)

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											tca Ser					154
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											cct Pro					250
aaa Lys	ttg Leu	gta Val 70	gaa Glu	cat His	gtc Val	cct Pro	999 Gly 75	cag Gln	cct Pro	gtg Val	agg Arg	aac Asn 80	ccg Pro	cag Gln	tgt Cys	298
cga Arg	atc Ile 85	tgc Cys	aat Asn	caa Gln	aac Asn	agc Ser 90	agc Ser	aat Asn	cca Pro	aac Asn	cag Gln 95	aga Arg	cac His	ccg Pro	att Ile	346
aca Thr 100	aat Asn	gct Ala	att Ile	gat Asp	gga Gly 105	aag Lys	aac Asn	act Thr	tgg Trp	tgg Trp 110	cag Gln	agt Ser	ccc Pro	agt Ser	att Ile 115	394
aag Lys	aat Asn	gga Gly	atc Ile	gaa Glu 120	tac Tyr	cat His	tat Tyr	gtg Val	aca Thr 125	att Ile	aca Thr	ctg Leu	gat Asp	tta Leu 130	cag Gln	442
cag Gln	gtg Val	ttc Phe	cag Gln 135	atc Ile	gcg Ala	tat Tyr	gtg Val	att Ile 140	gtg Val	aag Lys	gca Ala	gct Ala	aac Asn 145	tcc Ser	ccc Pro	490
cgg Arg	cct Pro	gga Gly 150	aac Asn	tgg Trp	att Ile	ttg Leu	gaa Glu 155	cgc Arg	tct Ser	ctt Leu	gat Asp	gat Asp 160	gtt Val	gaa Glu	tac Tyr	538
aag Lys	ccc Pro 165	tgg Trp	cag Gln	tat Tyr	cat His	gct Ala 170	gtg Val	aca Thr	gac Asp	acg Thr	gag Glu 175	tgc Cys	cta Leu	acg Thr	ctt Leu	586
tac Tyr 180	aat Asn	att Ile	tat Tyr	ccc Pro	cgc Arg 185	act Thr	ggg Gly	cca Pro	ccg Pro	tca Ser 190	tat Tyr	gcc Ala	aaa Lys	gat Asp	gat Asp 195	634
gag Glu	gtc Val	atc Ile	tgc Cys	act Thr 200	tca Ser	ttt Phe	tac Tyr	tcc Ser	aag Lys 205	Ile	cac His	ccc Pro	tta Leu	gaa Glu 210	aat Asn	682
gga Gly	gag Glu	att Ile	cac His 215	atc Ile	tct Ser	tta Leu	atc Ile	aat Asn 220	Gly	aga Arg	cca Pro	agt Ser	gcc Ala 225	gat Asp	gat Asp	730
cct Pro	tct Ser	cca Pro 230	Glu	ctg Leu	cta Leu	gaa Glu	ttt Phe 235	Thr	tcc Ser	gct Ala	cgc Arg	tat Tyr 240	Ile	cgc Arg	ctg Leu	778

aga Arg	ttt Phe 245	cag Gln	agg Arg	atc Ile	cgc Arg	aca Thr 250	ctg Leu	aat Asn	gct Ala	gac Asp	ttg Leu 255	atg Met	atg Met	ttt Phe	gct Ala	826
				aga Arg												874
tac Tyr	tcg Ser	gtc Val	aag Lys	gat Asp 280	att Ile	tca Ser	gtt Val	gga Gly	999 Gly 285	atg Met	tgc Cys	atc Ile	tgc Cys	tat Tyr 290	ggt Gly	922
				tgt Cys												970
				aac Asn												1018
				aaa Lys												1066
				tgc Cys												1114
				gcc Ala 360												1162
				ggt Gly												1210
				aca Thr												1258
				cca Pro												1306
				gaa Glu												1354
				gga Gly 440												1402
				tgt Cys												1450
				agt Ser												1498
ggc	ccc	tgt	atc	tgc	aag	gaa	aat	gtt	gaa	gga	gga	gac	tgt	agt	cgt	1546

Gly	Pro 485	Cys	Ile	Cys	Lys	Glu 490	neA	Val	Glu	Gly	Gly 495	Asp	Cys	Ser	Arg	
											aat Asn					1594.
											tgt Cys					1642
											tgg Trp					1690
											gac Asp					1738
											cgg Arg 575					1786
											ctg Leu					1834
cca Pro	gca Ala	gta Val	gga Gly	gga Gly 600	cag Gln	ttg Leu	aca Thr	ttt Phe	acc Thr 605	ata Ile	tca Ser	tat Tyr	gac Asp	ctt Leu 610	gaa Glu	1882
											ctt Leu					1930
gag	ggt	aat	gac	tta	agc	atc	agc	aca	gcc	caa	gat	gag	gtg	tac	ctg	1978
GIU	Gly	Asn 630	Asp	Leu	Ser	Ile	Ser 635	Thr	Ala	GIn	Asp	Glu 640	Val	Tyr	Leu	
cac	cca	Asn 630 tct	Asp	Leu gaa	cat	act	635 aat	gta	ttg	tta	ctt Leu 655	640 aaa	gaa	gaa	tca	2026
cac His	cca Pro 645	Asn 630 tct Ser	Asp gaa Glu cat	gaa Glu	cat His	act Thr 650	635 aat Asn	gta Val cca	ttg Leu gtc	tta Leu cgt	ctt Leu	aaa Lys	gaa Glu gaa	gaa Glu ttt	tca Ser atg	2026
cac His ttt Phe 660	cca Pro 645 acc Thr	Asn 630 tct Ser ata Ile	Asp gaa Glu cat His	gaa Glu ggc Gly	cat His aca Thr 665	act Thr 650 cat His	aat Asn ttt Phe	gta Val cca Pro	ttg Leu gtc Val	tta Leu cgt Arg 670	ctt Leu 655 aga	aaa Lys aag Lys	gaa Glu gaa Glu aca	gaa Glu ttt Phe	tca Ser atg Met 675	
cac His ttt Phe 660 aca Thr	cca Pro 645 acc Thr gtg Val	Asn 630 tct ser ata Ile ctt Leu	Asp gaa Glu cat His gcg Ala	gaa Glu ggc Gly aat Asn 680	cat His aca Thr 665 ttg Leu	act Thr 650 cat His aag Lys	aat Asn ttt Phe aga Arg	gta Val cca Pro gtc Val	ttg Leu gtc Val ctc Leu 685	tta Leu cgt Arg 670 cta Leu	ctt Leu 655 aga Arg	aaa Lys aag Lys atc Ile	gaa Glu gaa Glu aca Thr	gaa Glu ttt Phe tac Tyr 690	tca Ser atg Met 675 agc Ser	2074
cac His ttt Phe 660 aca Thr ttt Phe	cca Pro 645 acc Thr gtg Val ggg Gly	Asn 630 tct Ser ata Ile ctt Leu atg Met	gaa Glu cat His gcg Ala gat Asp 695	gaa Glu ggc Gly aat Asn 680 gcc Ala	cat His aca Thr 665 ttg Leu atc	act Thr 650 cat His aag Lys ttc Phe	aat Asn ttt Phe aga Arg agg Arg	gta Val cca Pro gtc Val ttg Leu 700	ttg Leu gtc Val ctc Leu 685 agc Ser	tta Leu cgt Arg 670 cta Leu tct Ser	ctt Leu 655 aga Arg caa Gln	aaa Lys aag Lys atc Ile aac Asn	gaa Glu gaa Glu aca Thr ctt Leu 705 gta	gaa Glu ttt Phe tac Tyr 690 gaa Glu	tca Ser atg Met 675 agc Ser tcc Ser	2074

	725					730					735					
cct Pro 740	agg Arg	cac His	agg Arg	cga Arg	gtt Val 745	aac Asn	ggc Gly	act Thr	att Ile	ttt Phe 750	ggt Gly	ggc Gly	atc Ile	tgt Cys	gag Glu 755	2314
cca Pro	tgt Cys	cag Gln	tgc Cys	ttt Phe 760	ggt Gly	cat His	gcg Ala	gag Glu	tcc Ser 765	tgt Cys	gat Asp	gac Asp	gtc Val	act Thr 770	gga Gly	2362
gaa Glu	tgc Cys	ctg Leu	aac Asn 775	tgt Cys	aag Lys	gat Asp	cac His	aca Thr 780	ggt Gly	ggc Gly	cca Pro	tat Tyr	tgt Cys 785	gat Asp	aaa Lys	2410
tgt Cys	ctt Leu	cct Pro 790	ggt Gly	ttc Phe	tat Tyr	ggc Gly	gag Glu 795	cct Pro	act Thr	aaa Lys	gga Gly	acc Thr 800	tct Ser	gaa Glu	gac Asp	2458
			tgt Cys													2506
cca Pro 820	acg Thr	tgc Cys	cat His	tta Leu	gac Asp 825	cgg Arg	agt Ser	ctt Leu	gga Gly	ttg Leu 830	atc Ile	tgt Cys	gat Asp	gga Gly	tgc Cys 835	2554
			tac Tyr													2602
			CCC Pro 855													2650
			ctt Leu													2698
			ctg Leu													2746
			gat Asp													2794
			cgc Arg													2842
			gga Gly 935													2890
tgt Cys	gac Asp	aaa Lys 950	tgc Cys	aag Lys	gct Ala	ggg Gly	acc Thr 955	ttt Phe	ggc Gly	cta Leu	caa Gln	tca Ser 960	gca Ala	agg Arg	ggc Gly	2938
			tgc Cys													2986

				caa Gln												3034
			Сув	gcc Ala 1000				Phe					Gly			3082
		Cys		tgt Cys			Leu					Asp				3130
ggg Gly	Arg	tgc Cys 1030	att Ile	tgc Cys	cca Pro	Pro	aat Asn 1035	acc Thr	att Ile	gga Gly	Glu	aaa Lys 1040	tgt Cys	tct Ser	aaa Lys	3178
Cys	gca Ala 1045	ccc Pro	aat Asn	acc Thr	Trp	ggc Gly L050	cac His	agc Ser	att Ile	Thr	act Thr 1055	ggt Gly	tgt Cys	aag Lys	gct Ala	3226
	Asn			aca Thr					Asp					Val		3274
aca Thr	ggc Gly	caa Gln	Cys	aac Asn 1080	tgt av2	cat His	cca Pro	Lys	ttc Phe 1085	tct Ser	ggt Gly	gca Ala	Lув	tgt Cys 1090	aca Thr	3322
gag Glu	tgc Cys	Ser	cga Arg 1095	ggt Gly	cac His	tgg Trp	Asn	tac Tyr 1100	cct Pro	cgc Arg	tgc Cys	Asn	ctc Leu 1105	tgt Cys	gac Asp	3370
tgc Cys	Phe	ctc Leu 1110	cct Pro	Gly ggg	aca Thr	Asp	gcc Ala 1115	aca Thr	acc Thr	tgt Cys	Asp	tca Ser 1120	gag Glu	act Thr	aaa Lys	3418
Lys	tgc Cys 1125	tcc Ser	tgt Cys	agt Ser	Asp	caa Gln 1130	act Thr	ggg Gly	cag Gln	Cys	act Thr 1135	tgt Cys	aag Lys	gtg Val	aat Asn	3466
Val 114	Glu 0	Gly	Ile		Cys 1145	Asp	Arg	Сув	Arg	Pro 1150	Gly	ГÀЗ	Phe	Gly	Leu 1155	3514
gat Asp	gcc Ala	aag Lys	Asn	cca Pro 1160	ctt Leu	ggc	tgc Cys	Ser	agc Ser 1165	Cys	tat Tyr	tgc Cys	ttc Phe	ggc Gly 11 <b>7</b> 0	Thr	3562
act Thr	acc Thr	Gln	tgc Сув 1175		gaa Glu	gca Ala	Lys	gga Gly 1180	Leu	atc Ile	cgg Arg	Thr	tgg Trp 1185	Val	act Thr	3610
ctg Leu	Lys	gct Ala 1190	Glu	cag Gln	acc Thr	att Ile	cta Leu 1195	Pro	ctg Leu	gta Val	gat Asp	gag Glu 1200	Ala	ctg Leu	cag Gln	3658
cac His	acg Thr 1205	Thr	acc	Lys Lys	Gly	att Ile 1210	Val	ttt Phe	caa Gln	cat His	cca Pro 1215	Glu	att Ile	gtt Val	gcc Ala	3706

	Met			Met					cat His 1					Tyr		3754
			Glu					Lys	aag Lys 245				Tyr			3802
aaa Lys	ctc Leu	Lys	tat Tyr 255	gca Ala	atc Ile	tat Tyr	Phe	gag Glu 260	gct Ala	cgg Arg	gaa Glu	Glu	aca Thr 265	ggt Gly	ttc Phe	3850
	Thr					Val			cga Arg		Gly					3898
Ala	aga Arg 285	att Ile	atc Ile	gtc Val	Arg	cat His 290	atg Met	gct Ala	gct Ala	Pro	ctg Leu L295	att Ile	ggc	caa Gln	ttg Leu	3946
	Arg			Ile					aaa Lys					Tyr		3994
gat Asp	gat Asp	cct Pro	Arg	gtc Val 1320	cat His	aga Arg	act Thr	Val	acc Thr 1325	cga Arg	gaa Glu	gac Asp	Phe	ttg Leu 1330	gat Asp	4042
		Tyr					Ile		atc Ile			Thr				4090
ttc Phe	Met	cga Arg 1350	caa Gln	agc Ser	agg Arg	Ile	tct Ser 1355	gaa Glu	atc Ile	tca Ser	Met	gag Glu 1360	gta Val	gct Ala	gaa Glu	4138
Gln	gga Gly 1365	cgt Arg	gga Gly	aca Thr	Thr	atg Met 1370	act Thr	cct Pro	cca Pro	Ala	gac Asp 1375	ttg Leu	att Ile	gaa Glu	aaa Lys	4186
tgt Cys 1380	Asp	tgt Cys	ccc Pro	Leu	ggć Gly 1385	tat Tyr	tct Ser	ggc	ctg Leu	tcc Ser 1390	tgt Cys	gag Glu	gca Ala	Cys	ttg Leu 1395	4234
			Tyr					Gln	cca Pro 1405				Thr			4282
cca Pro	acc Thr	Leu	ggc Gly 1415	acc Thr	tgt Cys	gtt Val	Pro	tgt Cys 1420	caa Gln	tgt Cys	aat Asn	Gly	cac His 1425	agc Ser	agc Ser	4330
ctg Leu	Сув	gac Asp 1430	cct Pro	gaa Glu	aca Thr	Ser	ata Ile 1435	tgc Cys	cag Gln	aat Asn	Cys	caa Gln 1440	His	cac His	act Thr	4378
Ala	ggt Gly 1445	gac Asp	ttc Phe	tgt Cys	Glu	cga Arg 1450	tgt Cys	gct Ala	ctt Leu	Gly	tac Tyr 1455	Tyr	gga Gly	att Ile	gtc Val	4426
aag	gga	ttg	cca	aat	gac	tgt	cag	caa	tgt	gcc	tgc	cct	ctg	att	tct	4474

Lys 1460		Leu	Pro	Asn 1	Asp 465	Cys	Gln	Gln		Ala 470	Cys	Pro	Leu		Ser 475	
			Asn	ttc Phe 480				Cys					Leu			4522
		Суѕ		gct Ala			Arg					Gln				4570
	Суз			ggc Gly		Thr					Asn					4618
Сув				gag Glu	Сув					Ser						4666
gac Asp 1540	Pro	gtc Val	aca Thr	gga Gly	ttc Phe 1545	tgc Cys	acg Thr	tgc Cys	Arg	cct Pro 1550	gga Gly	gcc Ala	acg Thr	Cly	agg Arg 1555	4714
aag Lys	tgt Cys	gac Asp	Gly	tgc Cys 1560	aag Lys	cac His	tgg Trp	His	gca Ala 1565	cgc Arg	gag Glu	ggc Gly	Trp	gag Glu 1570	tgt Cys	4762
gtt Val	ttt Phe	Cys	gga Gly 1575	gat Asp	gag Glu	tgc Cys	Thr	ggc Gly 1580	ctt <b>Le</b> u	ctt Leu	ctc Leu	Gly	gac Asp 1585	ttg Leu	gct Ala	4810
cgc Arg	Leu	gag Glu 1590	cag Gln	atg Met	gtc Val	Met	agc Ser 1595	atc Ile	aac Asn	ctc Leu	Thr	ggt Gly 1600	ccg Pro	ctg Leu	ect Pro	4858
Ala	cca Pro 1605	tat Tyr	aaa Lys	atg Met	Leu	tat Tyr 1610	ggt Gly	ctt Leu	gaa Glu	Asn	atg Met 1615	act Thr	cag Gln	gag Glu	cta Leu	4906
aag Lys 1620	His	ttg Leu	ctg Leu	tca Ser	cct Pro 1625	cag Gln	cgg Arg	gcc Ala	Pro	gag Glu 1630	agg Arg	ctt Leu	att Ile	Gln	ctg Leu 1635	4954
gca Ala	gag Glu	ggc Gly	Asn	ctg Leu 1640	aat Asn	aca Thr	ctc Leu	Val	acc Thr 1645	gaa Glu	atg Met	aac Asn	Glu	ctg Leu 1650	ctg L <b>e</b> u	5002
acc Thr	agg Arg	Ala	acc Thr 1655	aaa Lys	gtg Val	aca Thr	Ala	gat Asp 1660	ggc Gly	gag Clu	cag Gln	Thr	gga Gly 1665	cag Gln	gat Asp	5050
gct Ala	Glu	agg Arg 1670	Thr	aac Asn	aca Thr	Arg	gca Ala 1675	aag <b>L</b> ys	tcc Ser	ctg Leu	Gly	gaa Glu 1680	ttc Phe	att Ile	aag Lys	5098
Glu	ctt Leu 1685	Ala	cgg Arg	gat Asp	Ala	gaa Glu 1690	gct Ala	gta Val	aat Asn	Glu	aaa Lys 1695	Ala	ata Ile	aaa Lys	cta Leu	5146
aat Asn	gaa Glu	act Thr	cta Leu	gga Gly	act Thr	cga Arg	gac Asp	gag Glu	gcc Ala	ttt Phe	gag Glu	aga Arg	aat Asn	ttg Leu	gaa Glu	5194

1700	1705	1710	. 1715
ggg ctt cag aaa gag Gly Leu Gln Lys Glu 1720	att gac cag ato	g att aaa gaa ctg	agg agg aaa 5242
aat cta gag aca caa Asn Leu Glu Thr Gln 1735		a Glu Asp Glu Leu	
gaa gcc ctt ctg aaa Glu Ala Leu Leu Lys 1750	aaa gtg aag aag Lys Val Lys Lys 1755	g ctg ttt gga gag s Leu Phe Gly Glu 1760	tcc cgg ggg 5338 Ser Arg Gly
gaa aat gaa gaa atg Glu Asn Glu Glu Met 1765			
aaa aac aaa gtt gat Lys Asn Lys Val Asp 1780			
aaa atc aga gaa gct Lys Ile Arg Glu Ala 1800	Asn Arg Leu Phe		
act gca ttg gag aaa Thr Ala Leu Glu Lys 1815		a Val Glu Ser Gly	
att gag aac act tta Ile Glu Asn Thr Leu 1830			
cgt ctt gca gat gaa Arg Leu Ala Asp Glu 1845			
caa act aaa ttg cca Gln Thr Lys Leu Pro 1860			
gac ctc tcc caa gaa Asp Leu Ser Gln Glu 1880			
cag gct gag agc cac Gln Ala Glu Ser His 1895		Asn Asp Ser Ser	
gat gga atc ctt gat Asp Gly Ile Leu Asp 1910			
gcc ttc aaa gct tac Ala Phe Lys Ala Tyr 1925			
aaa gtt gcc aaa gaa Lys Val Ala Lys Glu 1940			

	cet egg ggt to Pro Arg Gly Lo 1960		Asp Ala Lys (		5962
Gln Lys Ser	ttc agg att c Phe Arg Ile Lo .975		Lys Lys Leu A		6010
	aat gaa gac c Asn Glu Asp H				6058
	gct aga aat g Ala Arg Asn G 20	ly Asp Leu Leu			6106
ttg gga aag Leu Gly Lys 2020	tta tca gct a Leu Ser Ala I 2025	tt cca aat gat le Pro Asn Asp	aca gct gct o Thr Ala Ala : 2030	aaa ctg caa Lys Leu Gln 2035	6154
gct gtt aag Ala Val Lys	gac aaa gcc a Asp Lys Ala A 2040	ga caa gcc aac rg Gln Ala Asr 2045	Asp Thr Ala	aaa gat gta Lys Asp Val 2050	6202
Leu Ala Gln	att aca gag c Ile Thr Glu L 2055	tc cac cag aac eu His Gln Asr 2060	Leu Asp Gly	ctg aag aag Leu Lys Lys 065	6250
	aaa cta gca g Lys Leu Ala A				6298
aaa gat cct Lys Asp Pro 2085	tcc aag aac a Ser Lys Asn L 20	aa atc att gco ys Ile Ile Ala 90	gat gca gat Asp Ala Asp 2095	gcc act gtc Ala Thr Val	6346
aaa aat tta Lys Asn Leu 2100	gaa cag gaa g Glu Gln Glu A 2105	ct gac cgg cta la Asp Arg Lev	a ata gat aaa 1 Ile Asp Lys 2110	ctc aaa ccc Leu Lys Pro 2115	6394
atc aag gaa Ile Lys Glu	ctt gag gat a Leu Glu Asp A 2120	ac cta aag aaa sn Leu Lys Lys 2129	Asn Ile Ser	gag ata aag Glu Ile Lys 2130	6442
Glu Leu Ile	aac caa gct c Asn Gln Ala A 2135	gg aaa caa gco rg Lys Gln Ala 2140	a Asn Ser Ile	aaa gta tct Lys Val Ser 145	6490
gtg tct tca Val Ser Ser 2150	gga ggt gac t Gly Gly Asp C	gc att cga act ys Ile Arg Th: 2155	a tac aaa cca r Tyr Lys Pro 2160	gaa atc aag Glu Ile Lys	6538
aaa gga agt Lys Gly Ser 2165	tac aat aat a Tyr Asn Asn I 21	tt gtt gtc aad le Val Val Asi 70	gta aag aca n Val Lys Thr 2175	gct gtt gct Ala Val Ala	6586
gat aac ctc Asp Asn Leu 2180	ctc ttt tat c Leu Phe Tyr I 2185	tt gga agt gc eu Gly Ser Al	c aaa ttt att a Lys Phe Ile 2190	gac ttt ctg Asp Phe Leu 2195	6634

			Met			ggc Gly		Val					Asp			6682
		Val				gag Glu	Tyr					Ile				6730
	Trp					gca Ala 2					Arg					6778
Ser					Asp	gga Gly 250				Ser						6826
cac His 2260	His	tcg Ser	acg Thr	Ser	cct Pro 265	cca Pro	61Å 888	tac Tyr	Thr	att Ile 270	cta Leu	gat Asp	gtg Val	Asp	gca Ala 2275	6874
			Leu			ggt Gly		Leu					Lys			6922
gat Asp	gct Ala	Val	cgt Arg 2295	gtg Val	att Ile	aca Thr	Phe	act Thr 2300	ggc Gly	tgc Cys	atg Met	Gly	gaa Glu 2305	aca Thr	tac Tyr	6970
	Asp					ggt Gly					Arg					7018
Asp	tgc Cys 2325	aaa Lys	gga Gly	tgc Cys	Thr	gtc Val 2330	agt Ser	cct Pro	cag Gln	Val	gaa Glu 2335	gat Asp	agt Ser	gag Glu	GJA BBB	7066
act Thr 234	Ile	caa Gln	ttt Phe	Asp	gga Gly 2345	gaa Glu	ggt Gly	tat Tyr	Ala	ttg Leu 2350	gtc Val	agc Ser	cgt Arg	Pro	att Ile 2355	7114
cgc Arg	tgg Trp	tac Tyr	Pro	aac Asn 2360	atc Ile	tcc Ser	act Thr	Val	atg Met 2365	ttc Phe	aag Lys	ttc Phe	Arg	aca Thr 2370	ttt Phe	7162
		Ser				atg Met	Tyr					Asp				7210
	Met					act Thr					Lys					7258
Leu	ggc Gly 2405	tca Ser	gga Gly	atg Met	Ala	tcc Ser 2410	gtt Val	gtc Val	agc Ser	Asn	caa Gln 2415	aac Asn	cat His	aat Asn	gat Asp	7306
	Гуs			Ser		act Thr			Arg					Ala		7354
ata	tca	att	gta	gat	ata	gat	act	aat	cag	gag	gag	aat	ata	gca	act	7402

2440 2445	Slu Glu Asn Ile Ala Thr 2450
tog tot tot gga aac aac ttt ggt ott gac t Ser Ser Ser Gly Asn Asn Phe Gly Leu Asp L 2455 2460	etg aaa gca gat gac aaa 7450 eu Lys Ala Asp Asp Lys 2465
ata tat ttt ggt ggc ctg cca acg ctg aga a Ile Tyr Phe Gly Gly Leu Pro Thr Leu Arg A 2470 2475	
agg cca gaa gta aat ctg aag aaa tat tcc g Arg Pro Glu Val Asn Leu Lys Lys Tyr Ser G 2485 2490	
gaa att tca aga act ccg tac aat ata ctc a Glu Ile Ser Arg Thr Pro Tyr Asn Ile Leu S 2500 2505 25	ggt agt ccc gat tat gtt 7594 Ser Ser Pro Asp Tyr Val 510 2515
ggt gtt acc aaa gga tgt tcc ctg gag aat g Gly Val Thr Lys Gly Cys Ser Leu Glu Asn V 2520 2525	
cct aag cct ggt ttt gtg gag ctc tcc cct g Pro Lys Pro Gly Phe Val Glu Leu Ser Pro V 2535 2540	
aca gaa atc aac ctg tca ttc agc acc aag a Thr Glu Ile Asn Leu Ser Phe Ser Thr Lys A 2550 2555	
att the	
Leu Leu Gly Ser Gly Gly Thr Pro Ala Pro P 2565 2570	ct agg aga aaa cga agg 7786 Pro Arg Arg Lys Arg Arg 2575
Leu Leu Gly Ser Gly Gly Thr Pro Ala Pro P 2565 2570 cag act gga cag gcc tat tat gta ata ctc c Gln Thr Gly Gln Ala Tyr Tyr Val Ile Leu L	Pro Arg Arg Lys Arg Arg 2575 etc aac agg ggc cgt ctg 7834
Leu Leu Gly Ser Gly Gly Thr Pro Ala Pro P 2565 2570 cag act gga cag gcc tat tat gta ata ctc c Gln Thr Gly Gln Ala Tyr Tyr Val Ile Leu L	2575  Arg Arg Lys Arg Arg 2575  Arc aac agg ggc cgt ctg 7834  Leu Asn Arg Gly Arg Leu 2595  Arg agg aaa att gtc atc 7882
Leu Leu Gly Ser Gly Gly Thr Pro Ala Pro P 2565  cag act gga cag gcc tat tat gta ata ctc c Gln Thr Gly Gln Ala Tyr Tyr Val Ile Leu L 2580  2585  gaa gtg cat ctc tcc aca ggg gca cga aca a Glu Val His Leu Ser Thr Gly Ala Arg Thr M	2575 2575 2575 2575 2575 2575 2575 2575
Leu Leu Gly Ser Gly Gly Thr Pro Ala Pro Pro 2565 2570  cag act gga cag gcc tat tat gta ata ctc con 2580 2585 2580  gaa gtg cat ctc tcc aca ggg gca cga aca and Glu Val His Leu Ser Thr Gly Ala Arg Thr Mark 2600 2605  aga cca gag ccg aat ctg ttt cat gat gga and Arg Pro Glu Pro Asn Leu Phe His Asp Gly Ala	Pro Arg Arg Lys Arg Arg 2575  The aac agg gge egt etg 3834  The Arg Gly Arg Leu 2595  The agg aaa att gte atc 3882  The Arg Lys Ile Val Ile 2610  The agg aaa cat tee gtt cat 3893  The agg aga cat tee gtt cat 3893  The agg aga cat tee gtt cat 3893  The agg aga aga aga aga 3893  The agg aga aga aga aga 3893
Leu Leu Gly Ser Gly Gly Thr Pro Ala Pro Pro 2565 2570  cag act gga cag gcc tat tat gta ata ctc con Gln Thr Gly Gln Ala Tyr Tyr Val Ile Leu Lou 2580 2585 25  gaa gtg cat ctc tcc aca ggg gca cga aca a Glu Val His Leu Ser Thr Gly Ala Arg Thr Monday 2600 2605  aga cca gag ccg aat ctg ttt cat gat gga and Arg Pro Glu Pro Asn Leu Phe His Asp Gly Ala Arg Thr Arg Gly Ile Phe Thr Val Gly Val Glu Arg Thr Arg Gly Ile Phe Thr Val Gly Val Glu Arg Thr Arg Gly Ile Phe Thr Val Gly	Pro Arg Arg Lys Arg Arg 2575  The aac agg gge egt etg 7834  Leu Asn Arg Gly Arg Leu 2595  The agg aaa att gte atc 2510  The Arg Lys Ile Val Ile 2610  The agg gaa cat tee gtt cat 2625  The agg gaa aac aga 7978  The agg gat gaa aac aga 2640  The aga gtt aaa aag 8026
Leu Leu Gly Ser Gly Gly Thr Pro Ala Pro Pro 2565 2570  cag act gga cag gcc tat tat gta ata ctc common commo	Pro Arg Arg Lys Arg Arg 2575  Ltc aac agg ggc cgt ctg 3834 Leu Asn Arg Gly Arg Leu 2595  Ltg agg aaa att gtc atc 2595  Ltg agg aaa att gtc atc 2610  Ltg aga cat tcc gtt cat 2610  Ltg Glu His Ser Val His 2625  Lta agt gat gaa aac aga 2640  Ltg atc gaa gtt aaa aag 2640  Ltg atc gaa gtt aaa aag 2655  Lta acct tcc cca ctc aga 2674

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Pro Thr Pro Thr Pro		ggt cet tgt get gea gaa Gly Pro Cys Ala Ala Glu 2750	
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		acc aaa gtt aaa aac cgt Thr Lys Val Lys Asn Arg 2785	
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Gly Pro Val Thr Tyr		tgc gtc agg aat ctc cac Cys Val Arg Asn Leu His 2910	
	Asp Leu Glu Gln I	ecc acc tcc agc ttc cat Pro Thr Ser Ser Phe His 925 2930	

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Met 65	Tyr	Cys	Lys	Leu	Val 70	Glu	His	Val	Pro	Gly 75	Gln	Pro	Val	Arg	Asn 80
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His	Pro	Ile	Thr 100	Asn	Ala	Ile	Asp	Gly 105	Lys	Asn	Thr	Trp	Trp 110	Gln	Ser
Pro	Ser	Ile 115	Lys	Asn	Gly	Ile	Glu 120	Tyr	His	Tyr	Val	Thr 125	Ile	Thr	Leu
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Lys	Asp	<b>Asp</b> 195	Glu	Val	Ile	Сув	Thr 200	Ser	Phe	Tyr	Ser	Lys 205	Ile	His	Pro
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Ala 225	Asp	Asp	Pro	Ser	Pro 230	Glu	Leu	Leu	Glu	Phe 235	Thr	Ser	Ala	Arg	Tyr 240
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Arg	Tyr	Tyr 275	Tyr	Ser	Val	Lys	Asp 280	Ile	Ser	Val	Gly	Gly 285	Met	Сув	Ile
Cys	Tyr 290	Gly	His	Ala	Arg	Ala 295	Сув	Pro	Leu	Asp	Pro 300	Ala	Thr	Asn	Lys
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Cys	Суз	Pro	Gly	Phe 325	His	Gln	Lys	Pro	Trp 330	Arg	Ala	Gly	Thr	Phe 335	Leu

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Cys Tyr Tyr Asp Glu Asn Val Ala Arg Arg Asn Leu Ser Leu Asn Ile

355 360 365

Arg Gly Lys Tyr Ile Gly Gly Gly Val Cys Ile Asn Cys Thr Gln Asn 370 \$375\$

Thr Ala Gly Ile Asn Cys Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro 385 390 395 400

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Leu Thr Asp Leu Pro Gly Arg Ile Arg Val Ala Pro Gln Asp Asp 545 550 550 560

Leu Asp Ser Pro Gln Gln Ile Ser Ile Ser Asn Ala Glu Ala Arg Gln 565 570 575

Ala Leu Pro His Ser Tyr Tyr Trp Ser Ala Pro Ala Pro Tyr Leu Gly 580 585 590

Asn Lys Leu Pro Ala Val Gly Gly Gln Leu Thr Phe Thr Ile Ser Tyr 595 600 605

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- Ile Val Ala His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro 1220 1225 1230
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- His His Thr Ala Gly Asp Phe Cys Glu Arg Cys Ala Leu Gly Tyr Tyr 1445 1450 1455
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- Glu Asp Ile Gln Thr Lys Leu Pro Pro Met Ser Glu Glu Leu Asn Asp 1860 1865 1870
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- Lys Val Ser Gln Ala Glu Ser His Ala Ala Gln Leu Asn Asp Ser Ser 1890 1895 1900
- Ala Val Leu Asp Gly Ile Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn 905 1910 1915 1920
- Ala Thr Ala Ala Phe Lys Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp 1925 1930 1935
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tta ttc cct gct gtc ctg aat ctt gct tct aat gct ctt atc acg acc 96 Leu Phe Pro Ala Val Leu Asn Leu Ala Ser Asn Ala Leu Ile Thr Thr

aat gca aca tgt gga gaa aaa gga cct gaa atg tac tgc aaa ttg gta 144 Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys Lys Leu Val

gaa cat gtc cct ggg cag cct gtg agg aac ccg cag tgt cga atc tgc 192 Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys Arg Ile Cys 50 55 60

	caa Gln															240
	gat Asp															288
	gaa Glu															336
	atc Ile															384
	tgg Trp 130															432
	tat Tyr															480
	ccc Pro															528
	act Thr															576
cac His	atc Ile	tct Ser 195	tta Leu	atc Ile	aat Asn	61y 999	aga Arg 200	cca Pro	agt Ser	gcc Ala	gat Asp	gat Asp 205	cct Pro	tct Ser	cca Pro	624
gaa Glu	ctg Leu 210	cta Leu	gaa Glu	ttt Phe	acc Thr	tcc Ser 215	gct Ala	cgc Arg	tat Tyr	att Ile	cgc Arg 220	ctg Leu	aga Arg	ttt Phe	cag Gln	672
	atc Ile															720
cca Pro	aga Arg	gaa Glu -	att Ile	gac Asp 245	ccc Pro	att Ile	gtc Val	acc Thr	aga Arg 250	aga Arg	tat Tyr	tac Tyr	tac Tyr	tcg Ser 255	gtc Val	768
aag Lys	gat Asp	att Ile	tca Ser 260	gtt Val	gga Gly	ggg Gly	atg Met	tgc Cys 265	atc Ile	tgc Cys	tat Tyr	ggt Gly	cat His 270	gcc Ala	agg Arg	816
gct Ala	tgt Cys	cca Pro 275	ctt Leu	gat Asp	cca Pro	gcg Ala	aca Thr 280	aat Asn	aaa Lys	tct Ser	cgc Arg	tgt Cys 285	gag Glu	tgt Cys	gag Glu	864
	aac Asn 290															912

	aaa Lys															960
	tgc Cys															1008
	gcc Ala															1056
	ggt Gly															1104
	aca Thr 370															1152
	cca Pro															1200
	gaa Glu															1248
Pro	gga Gly	Ser	Cys 420	His	Сув	Lys	Thr	Gly 425	Phe	Gly	Gly	Val	Ser 430	Cys	Авр	1296
cgg Arg	tgt Cys	gcc Ala 435	agg Arg	ggc Gly	tac Tyr	act Thr	ggc Gly 440	tac Tyr	ccg Pro	gac Asp	tgc Cys	aaa Lys 445	gcc Ala	tgt Cys	aac Asn	1344
tgc Cys	agt Ser 450	ggg Gly	tta Leu	ggg ggg	agc Ser	aaa Lys 455	aat Asn	gag Glu	gat Asp	cct Pro	tgt Cys 460	ttt Phe	ggc Gly	ccc Pro	tgt Cys	1392
ato Ile 465	tgc Cys	aag Lys	gaa Glu	aat Asn	gtt Val 470	gaa Glu	gga Gly	gga Gly	gac Asp	tgt Cys 475	agt Ser	cgt Arg	tgc Cys	aaa Lys	tcc Ser 480	1440
ggc Gly	ttc Phe	ttc Phe	aat Asn	ttg Leu 485	caa Gln	gag Glu	gat Asp	aat Asn	tgg Trp 490	aaa Lys	ggc Gly	tgc Cys	gat Asp	gag Glu 495	tgt Cys	1488
	tgt Cys			val										Thr		1536
ggo Gly	aaa Lys	ata Ile 515	caa Gln	gat Asp	atg Met	agt Ser	ggc Gly 520	tgg Trp	tat Tyr	ctg Leu	act Thr	gac Asp 525	ctt Leu	cct Pro	ggc Gly	1584
	att Ile 530															1632
ato	agc	atc	agt	aac	gcg	gag	gcc	cgg	caa	gcc	ctg	ccg	cac	agc	tac	1680

Ile 545	Ser	Ile	Ser	Asn	Ala 550	Glu	Ala	Arg	Gln	Ala 555	Leu	Pro	His	Ser	Туг 560	
tac Tyr	tgg Trp	agc Ser	gcg Ala	ccg Pro 565	gct Ala	ccc Pro	tat Tyr	ctg Leu	gga Gly 570	aac Asn	aaa Lys	ctc <b>Le</b> u	cca Pro	gca Ala 575	gta Val	1728
gga Gly	gga Gly	cag Gln	ttg Leu 580	aca Thr	ttt Phe	acc Thr	ata Ile	tca Ser 585	tat Tyr	gac Asp	ctt Leu	gaa Glu	gaa Glu 590	gag Glu	gaa Glu	1776
gaa Glu	gat Asp	aca Thr 595	gaa Glu	cgt Arg	gtt Val	ctc Leu	cag Gln 600	ctt Leu	atg Met	att Ile	atc Ile	tta Leu 605	gag Glu	ggt Gly	aat Asn	1824
gac Asp	ttg Leu 610	agc Ser	atc Ile	agc Ser	aca Thr	gcc Ala 615	caa Gln	gat Asp	gag Glu	gtg Val	tac Tyr 620	ctg Leu	cac His	cca Pro	tct Ser	1872
gaa Glu 625	gaa Glu	cat His	act Thr	aat Asn	gta Val 630	ttg Leu	tta Leu	ctt Leu	aaa Lys	gaa Glu 635	gaa Glu	tca Ser	ttt Phe	acc Thr	ata Ile 640	1920
	ggc Gly															1968
	aat Asn															2016
	gcc Ala															2064
	cct Pro 690															2112
cca Pro 705	cca Pro	g1y 999	tat Tyr	act Thr	ggc Gly 710	tcc Ser	tct Ser	tgt Cys	gaa Glu	tct Ser 715	tgt Cys	tgg Trp	cct Pro	agg Arg	cac His 720	2160
agg Arg	cga Arg	gtt Val	aac Asn	ggc Gly 725	act Thr	att Ile	ttt Phe	ggt Gly	ggc Gly 730	atc Ile	tgt Cys	gag Glu	cca Pro	tgt Cys 735	cag Gln	2208
	ttt Phe															2256
Cys aac		Gly aag	His 740 gat	Ala	Glu aca	Ser ggt	Cys ggc	Asp 745 cca	Asp tat	Val tgt	Thr gat	Gly aaa	Glu 750 tgt	Cys ctt	Leu cct	2304
Cys aac Asn ggt	Phe tgt	aag Lys 755	His 740 gat Asp	Ala cac His	Glu aca Thr	ggt Gly act	Gys ggc Gly 760 aaa	Asp 745 cca Pro	Asp tat Tyr acc	Val tgt Cys tct	Thr gat Asp gaa	aaa Lys 765 gac	Glu 750 tgt Cys	Cys ctt Leu caa	cct Pro	

785	790	795	800
cat tta gac cgg ag His Leu Asp Arg Se 80	r Leu Gly Leu	atc tgt gat gga tgc Ile Cys Asp Gly Cys 810	cct gtc ggg 2448 Pro Val Gly 815
tac aca gga cca cg Tyr Thr Gly Pro Ar 820	g Cys Glu Arg	tgt gca gaa ggc tat Cys Ala Glu Gly Tyr 825	ttt gga caa 2496 Phe Gly Gln 830
		cag cca tgc caa tgc Gln Pro Cys Gln Cys 845	
ctt gac ttc tcc at Leu Asp Phe Ser Il 850	c cct ggc agc e Pro Gly Ser 855	tgt gac agc ttg tct Cys Asp Ser Leu Ser 860	ggc tcc tgt 2592 Gly Ser C <b>ys</b>
		ggc cgg tac tgt gag Gly Arg Tyr Cys Glu 875	
gat gga tat ttt gg Asp Gly Tyr Phe Gl	y Asp Ala Val	gat gcg aag aac tgt Asp Ala Lys Asn Cys 890	cag ccc tgt 2688 Gln Pro Cys 895
	y Gly Ser Phe	tct gag gtt tgc cac Ser Glu Val Cys His 905	
gga cag tgt gag tg Gly Gln Cys Glu Cy 915	c aga gcc aac s Arg Ala Asn 920	gtt cag ggt cag aga Val Gln Gly Gln Arg 925	tgt gac aaa 2784 Cys Asp Lys
		caa tca gca agg ggc Gln Ser Ala Arg Gly 940	
tgc aac tgc aat to Cys Asn Cys Asn Se 945	r Phe Gly Ser 950	aag toa tto gac tgt Lys Ser Phe Asp Cys 955	gaa gag agt 2880 Glu Glu Ser 960
gga caa tgt tgg tg Gly Gln Cys Trp Cy 96	s Gln Pro Gly	gtc aca ggg aag aaa Val Thr Gly Lys Lys 970	tgt gac cgc 2928 Cys Asp Arg 975
		caa gaa gga ggc tgc Gln Glu Gly Gly Cys 985	
		tgt gac cca aag act Cys Asp Pro Lys Thr 1005	
		gag aaa tgt tct aaa Glu Lys Cys Ser Lys 1020	
		act ggt tgt aag gct Thr Gly Cys Lys Ala 1035	

agc Ser	aca Thr	gtg Val	gga Gly	tcc Ser 1045	ttg Leu	gat Asp	ttc Phe	Gln	tgc Cys 1050	aat Asn	gta Val	aat Asn	Thr	ggc Gly 1055	caa Gln	3168
tgc Cys	aac Asn	Cys	cat His 1060	cca Pro	aaa Lys	ttc Phe	Ser	ggt Gly 1065	gca Ala	aaa Lys	tgt Cys	Thr	gag Glu 1070	tgc Cys	agt Ser	3216
	Gly		tgg Trp			Pro					Cys					3264
Pro			gat Asp		Thr					Glu						3312
	Ser		caa Gln	Thr					Суя					Glu		3360
			gac Asp					Çly					Asp			3408
		Leu	ggc Gly 1140				Сув					Thr				3456
	Ser		gca Ala			Leu					Val					3504
Glu			att Ile		${\tt Pro}$					Ala						3552
	Lys		att Ile	Val					Glu					Met		3600
			gaa Glu					Glu					Lys			3648
		Phe	gaa Glu 1220				Leu					$\operatorname{Gly}$				3696
	Ala		tat Tyr			Ala					Gly					3744
Asn			gtg Val		Ile					Pro						3792
atc Ile 1269	Val	agg Arg	cat His	Met	gct Ala 1270	gct Ala	cct Pro	ctg Leu	Ile	ggc Gly 1275	caa Gln	ttg Leu	aca Thr	Arg	cat His 1280	3840

gaa att gaa atg aca gag aaa gaa tgg aaa tat tat ggg gat gat	3888
cga gtc cat aga act gtg acc cga gaa gac ttc ttg gat ata cta tat Arg Val His Arg Thr Val Thr Arg Glu Asp Phe Leu Asp Ile Leu Tyr 1300 1305 1310	3936
gat att cat tac att ctt atc aaa gct act tat gga aat ttc atg cga Asp Ile His Tyr Ile Leu Ile Lys Ala Thr Tyr Gly Asn Phe Met Arg 1315 1320 1325	3984
caa agc agg att tct gaa atc tca atg gag gta gct gaa caa gga cgt Gln Ser Arg Ile Ser Glu Ile Ser Met Glu Val Ala Glu Gln Gly Arg 1330 1335 1340	4032
gga aca aca atg act cct cca gct gac ttg att gaa aaa tgt gat tgt Gly Thr Thr Met Thr Pro Pro Ala Asp Leu Ile Glu Lys Cys Asp Cys 1345 1350 1355 1360	4080
ccc ctg ggc tat tct ggc ctg tcc tgt gag gca tgc ttg ccg gga ttt Pro Leu Gly Tyr Ser Gly Leu Ser Cys Glu Ala Cys Leu Pro Gly Phe 1365 1370 1375	4128
tat cga ctg cgt tct caa cca ggt ggc cgc acc cct gga cca acc ctg Tyr Arg Leu Arg Ser Gln Pro Gly Gly Arg Thr Pro Gly Pro Thr Leu 1380 1385 1390	4176
ggc acc tgt gtt cca tgt caa tgt aat gga cac agc agc ctg tgt gac Gly Thr Cys Val Pro Cys Gln Cys Asn Gly His Ser Ser Leu Cys Asp 1395	4224
cct gaa aca tcg ata tgc cag aat tgt caa cat cac act gct ggt gac Pro Glu Thr Ser Ile Cys Gln Asn Cys Gln His His Thr Ala Gly Asp 1410 1415 1420	4272
ttc tgt gaa cga tgt gct ctt gga tac tat gga att gtc aag gga ttg Phe Cys Glu Arg Cys Ala Leu Gly Tyr Tyr Gly Ile Val Lys Gly Leu 1425 1430 1435 1440	4320
cca aat gac tgt cag caa tgt gcc tgc cct ctg att tct tcc agt aac Pro Asn Asp Cys Gln Gln Cys Ala Cys Pro Leu Ile Ser Ser Ser Asn 1445 1450 1455	4368
aat ttc agc ccc tct tgt gtc gca gaa gga ctt gac gac tac cgc tgc Asn Phe Ser Pro Ser Cys Val Ala Glu Gly Leu Asp Asp Tyr Arg Cys 1460 1465 1470	4416
acg gct tgt cca cgg gga tat gaa ggc cag tac tgt gaa agg tgt gcc Thr Ala Cys Pro Arg Gly Tyr Glu Gly Gln Tyr Cys Glu Arg Cys Ala 1475 1480 1485	4464
cct ggc tat act ggc agt cca ggc aac cct gga ggc tcc tgc caa gaa Pro Gly Tyr Thr Gly Ser Pro Gly Asn Pro Gly Gly Ser Cys Gln Glu 1490 1495 1500	4512
tgt gag tgt gat ccc tat ggc tca ctg cct gtg ccc tgt gac cct gtc Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro Val Pro Cys Asp Pro Val 1505 1510 1515 1520	4560

			•	1525			Pro		1530					1535		
ggc	tgc Cys	гув	cac His 1540	tgg Trp	cat His	gca Ala	cgc Arg	gag Glu 1545	ggc	tgg Trp	gag Glu	Сув	gtt Val 1550	ttt Phe	tgt Cys	4656
gga Gly	qaA	gag Glu 1555	tgc Cys	act Thr	ggc Gly	Leu	ctt Leu 1560	ctc Leu	ggt Gly	gac Asp	Leu	gct Ala 1565	cgc Arg	ctg Leu	gag Glu	4704
Gln :	Met 1570	Val	Met	Ser	Ile	Asn 1575	ctc Leu	Thr	Gly	Pro	Leu 1580	Pro	Ala	Pro	Tyr	4752
1585	Met 5	Leu	Tyr	GIY	Leu 1590	Glu	aat Asn	Met	Thr	Gln 1595	Glu	Leu	Lys	His 1	Leu 1600	4800
Leu	Ser	Pro	Gin 1	Arg 1605	Ala	Pro	gag Glu	Arg	Leu L610	Ile	Gln	Leu	Ala	Glu 1615	Gly	4848
Asn	Leu	Asn 1	Thr 1620	Leu	Val	Thr		Met L625	Asn	Glu	Leu	Leu 1	Thr L630	Arg	Ala	4896
Thr	Lys 1	Val 1635	Thr	Ala	Asp	Gly	gag Glu L640	Gln	Thr	Gly	Gln	Asp 1645	Ala	Glu	Arg	4944
Thr	aac Asn 650	aca Thr	aga Arg	gca Ala	Lys	tcc Ser 1655	ctg Leu	gga Gly	gaa Glu	Phe	att Ile 1660	aag Lys	gag Glu	ctt Leu	gcc Ala	4992
cgg Arg 1669	Asp	gca Ala	gaa Glu	Ala	gta Val 1670	aat Asn	gaa Glu	aaa Lys	Ala	ata Ile 1675	aaa Lys	cta Leu	aat Asn	Glu	act Thr 1680	5040
Leu	Gly	Thr	Arg 1	Asp 685	Glu	Ala	ttt Phe	Glu	Arg 1690	Asn	Leu	Glu	Gly 1	Leu 1695	Gln	5088
Lys	Glu	Ile 1	700	Gln	Met	Ile		Glu 1705	Leu	Arg	Arg	Lys 1	Asn 1710	Leu	Glu	5136
aca Thr	Gln	aag Lys 715	gaa Glu	att Ile	gct Ala	Glu	gat Asp 1720	gag Glu	ttg Leu	gta Val	Ala	gca Ala .725	gaa Glu	gcc Ala	ctt <b>Leu</b>	5184
Leu 1	Lys .730	Lys	Val	Lys	Lys 1	Leu 1735	ttt Phe	Gly	Glu	Ser 1	Arg .740	Gly	Glu	Asn	Glu	5232
gaa Glu 1745	Met	gag Glu	aag Lys	Asp	CtC Leu .750	cgg Arg	gaa Glu	aaa Lys	Leu	gct Ala 755	gac Asp	tac Tyr	aaa Lys	Asn	aaa Lys .760	5280
gtt Val	gat Asp	gat Asp	gct Ala	tgg Trp	gac Asp	ctt Leu	ttg Leu	aga Arg	gaa Glu	gcc Ala	aca Thr	gat Asp	aaa Lys	atc Ile	aga Arg	5328

1765		1770	1775	
gaa gct aat cgc cta Glu Ala Asn Arg Leu 1780	Phe Ala Val			5376
gag aaa aag aag gag Glu Lys Lys Lys Glu 1795	gct gtt gag Ala Val Glu 1800	Ser Gly Lys Arg	caa att gag aac Gln Ile Glu Asn 805	5424
act tta aaa gaa ggo Thr Leu Lys Glu Gly 1810				5472
gat gaa atc aac tcc Asp Glu Ile Asn Ser 1825	atc ata gac Tle Ile Asp ' 1830	tat gtt gaa gac Tyr Val Glu Asp 1835	atc caa act aaa Ile Gln Thr Lys 1840	5520
ttg cca cct atg tct Leu Pro Pro Met Ser 1845	Glu Glu Leu .			5568
caa gaa ata aag gad Gln Glu Ile Lys Asp 1860	Arg Lys Leu .	gct gag aag gtg Ala Glu Lys Val 865	tcc cag gct gag Ser Gln Ala Glu 1870	5616
agc cac gca gct cag Ser His Ala Ala Glr 1875		Ser Ser Ala Val		5664
ctt gat gag gct aaa Leu Asp Glu Ala Lys 1890				5712
gct tac agc aat att Ala Tyr Ser Asn Ile 1905	aag gac tat Lys Asp Tyr 1910	att gat gaa gct Ile Asp Glu Ala 1915	gag aaa gtt gcc Glu Lys Val Ala 1920	5760
aaa gaa gcc aaa gat Lys Glu Ala Lys Asy 1929	Leu Ala His	gaa gct aca aaa Glu Ala Thr Lys 1930	ctg gca aca ggt Leu Ala Thr Gly 1935	5808
cct egg ggt tta tta Pro Arg Gly Leu Leu 1940	ı Lys Glu Asp	gcc aaa ggc tgt Ala Lys Gly Cys 945	ctt cag aaa agc Leu Gln Lys Ser 1950	5856
ttc agg att ctt aad Phe Arg Ile Leu Ass 1955		Lys Leu Ala Asn		5904
aat gaa gac cat cta Asn Glu Asp His Let 1970	a aat ggc tta u Asn Gly Leu 1975	aaa acc agg ata Lys Thr Arg Ile 1980	gaa aat gct gat Glu Asn Ala Asp	5952
gct aga aat ggg ga Ala Arg Asn Gly As 1985	t ctc ttg aga o Leu Leu Arg 1990	act ttg aat gac Thr Leu Asn Asp 1995	act ttg gga aag Thr Leu Gly Lys 2000	6000
tta tca gct att cc Leu Ser Ala Ile Pro 200	o Asn Asp Thr	gct gct aaa ctg Ala Ala Lys Leu 2010	caa gct gtt aag Gln Ala Val Lys 2015	6048

gac Asp	aaa Lys	Ala	aga Arg 2020	caa Gln	gcc Ala	aac Asn	Asp	aca Thr 2025	gct Ala	aaa Lys	gat Asp	Val	ctg Leu 2030	gca Ala	cag Gln	6096
	Thr				cag Gln	Asn					Lys					6144
Lys					gtc Val 2					Āla						6192
	Lys			Ile	att Ile 2070				Asp					Asn		6240
			Ala		cgg Arg			Asp					Ile			6288
		Asp			aag Lys		naA					Lys				6336
	Gln				caa Gln	Ala					Val					6384
Gly					cga Arg 2					Glu						6432
	Asn			Val	gtc Val 2150				Thr					Asn		6480
			Leu		agt Ser			Phe					Ala			6528
		Lys			gtc Val		Phe					Gly				6576
	Arg				cca Pro	qaA					Asp					6624
Arg					aga Arg					Gly						6672
	Leu			Pro	aaa Lys 230				Val					His		6720
			Pro		tac Tyr			Leu					Asn			6768

Leu Phe Val (	ggt ggc ctg a Gly Gly Leu ' 260	act ggg aaa Thr Gly Lys : 2265	tta aag aag gc Leu Lys Lys Al	t gat gct gta a Asp Ala Val 2270	6816
			gga gaa aca ta Gly Glu Thr Ty 228	r Phe Asp Asn	6864
	Gly Leu Trp 2		gaa aaa gaa gg Glu Lys Glu Gl 2300		6912
			gat agt gag gg Asp Ser Glu Gl 2315		6960
		Ala Leu Val	agc cgt ccc at Ser Arg Pro Il 330		7008
Pro Asn Ile S			ttc aga aca tt Phe Arg Thr Ph		7056
			gac ctg aga ga Asp Leu Arg As 236	p Phe Met Ser	7104
Val Glu Leu	Thr Asp Gly	His Ile Lys	gtc agt tac ga Val Ser Tyr As	t ctg ggc tca p Leu Gly Ser	7152
2370	2.	375	2380		
gga atg gct	tee gtt gte	agc aat caa	2380 aac cat aat ga Asn His Asn As 2395		7200
gga atg gct s Gly Met Ala s 2385 aaa tca ttc	tcc gtt gtc Ser Val Val 2390 act ctg tca	agc aat caa Ser Asn Gln aga att caa Arg Ile Gln	aac cat aat ga Asn His Asn As	sp Gly Lys Trp 2400 at ata tca att	7200 7248
gga atg gct g Gly Met Ala g 2385 aaa tca ttc g Lys Ser Phe g gta gat ata g Val Asp Ile	tcc gtt gtc Ser Val Val 2390 act ctg tca Thr Leu Ser 2405 gat act aat	agc aat caa Ser Asn Gln aga att caa Arg Ile Gln 2 cag gag gag	aac cat aat ga Asn His Asn As 2395 aaa caa gcc aa Lys Gln Ala As	that at a to att on lle Ser lle 2415	
gga atg gct s Gly Met Ala s 2385  aaa tca ttc s Lys Ser Phe s  gta gat ata s Val Asp Ile s  gga aac aac s	tcc gtt gtc Ser Val Val 2390 act ctg tca Thr Leu Ser 2405 gat act aat Asp Thr Asn 420 ttt ggt ctt	agc aat caa Ser Asn Gln aga att caa Arg Ile Gln 2 cag gag gag Gln Glu Glu 2425 gac ttg aaa	aac cat aat ga Asn His Asn As 2395 aaa caa gcc aa Lys Gln Ala As 410 aat ata gca ac	the Gly Lys Trp 2400  at ata tca att in Ile Ser Ile 2415  at tcg tct tct ir Ser Ser Ser 2430  at ata tat ttt is Ile Tyr Phe	7248
gga atg gct g Gly Met Ala : 2385 aaa tca ttc t Lys Ser Phe : gta gat ata y Val Asp Ile : gga aac aac Gly Asn Asn : 2435 ggt ggc ctg g	act ctg tca Thr Leu Ser 2405 gat act aat Asp Thr Asn 420  ttt ggt ctt Phe Gly Leu  cca acg ctg Pro Thr Leu	agc aat caa Ser Asn Gln aga att caa Arg Ile Gln 2 cag gag gag Gln Glu Glu 2425 gac ttg aaa Asp Leu Lys 2440 aga aac ttg	aac cat aat ga Asn His Asn As 2395  aaa caa gcc aa Lys Gln Ala As 410  aat ata gca ac Asn Ile Ala Th gca gat gac aa Ala Asp Asp Ly	the Gly Lys Trp 2400  at ata tca att an Ile Ser Ile 2415  at tcg tct tct ar Ser Ser Ser 2430  at ata tat ttt as Ile Tyr Phe as agg cca gaa	7248 7296
gga atg gct galled gct	act ctg tca Thr Leu Ser 2405 gat act aat Asp Thr Asn 420 ttt ggt ctt Phe Gly Leu cca acg ctg Pro Thr Leu 2 aag aaa tat	agc aat caa Ser Asn Gln  aga att caa Arg Ile Gln  2  cag gag gag Gln Glu Glu 2425  gac ttg aaa Asp Leu Lys 2440  aga aac ttg Arg Asn Leu 455  tcc ggc tgc	aac cat aat ga Asn His Asn As 2395  aaa caa gcc aa Lys Gln Ala As 410  aat ata gca ac Asn Ile Ala Tr gca gat gac aa Ala Asp Asp Ly 244 agt atg aaa gc Ser Met Lys Al	the Gly Lys Trp 2400  at ata tca att tin Ile Ser Ile 2415  at tcg tct tct tr Ser Ser Ser 2430  at ata tat ttt tr Ile Tyr Phe ts Ile Tyr Phe t	7248 7296 7344
gga atg gct g Gly Met Ala s 2385  aaa tca ttc Lys Ser Phe s  gta gat ata y Val Asp Ile s gga aac aac Gly Asn Asn s 2435 ggt ggc ctg Gly Gly Leu s 2450 gta aat ctg Val Asn Leu s 2465 aga act ccg	tcc gtt gtc Ser Val Val 2390  act ctg tca 2405  gat act aat Asp Thr Asn 420  ttt ggt ctt Phe Gly Leu  cca acg ctg Pro Thr Leu 2  aag aaa tat Lys Lys Tyr 2470  tac aat aat	agc aat caa Ser Asn Gln  aga att caa Arg Ile Gln  2  cag gag gag Gln Glu Glu 2425  gac ttg aaa Asp Leu Lys 2440  aga aac ttg Arg Asn Leu 455  tcc ggc tgc Ser Gly Cys  ctc agt agt Leu Ser Ser	aac cat aat ga Asn His Asn As 2395  aaa caa gcc aa Lys Gln Ala As 410  aat ata gca ac Asn Ile Ala Tr gca gat gac aa Ala Asp Asp Ly 244 agt atg aaa gc Ser Met Lys Al 2460  ctc aaa gat at Leu Lys Asp Il	the Gly Lys Trp 2400  at ata tca att an Ile Ser Ile 2415  at tcg tct tct ar Ser Ser Ser 2430  at ata tat ttt ar agg cca gaa a Arg Pro Glu  at gaa att tca ate Glu Ile Ser 2480  at ggt gtt acc	7248 7296 7344 7392

Lys	Glγ	Cys	Ser 2500	Leu	Glu	Asn	Val	Tyr 2505	Thr	Val	Ser		Pro 2510	Lys	Pro	
ggt Gly	Phe	gtg Val 2515	gag Glu	ctc Leu	tcc Ser	Pro	gtg Val 2520	cca Pro	att Ile	gat Asp	Val	gga Gly 2525	aca Thr	gaa Glu	atc Ile	7584
Asn	ctg Leu 2530	tca Ser	ttc Phe	agc Ser	Thr	aag Lys 2535	aat Asn	gag Glu	tcc Ser	Gly	atc Ile 2540	att Ile	ctt Leu	ttg Leu	gga Gly	7632
agt Ser 254!	GLY	Gly 999	aca Thr	Pro	gca Ala 2550	cca Pro	cct Pro	agg Arg	Arg	aaa Lys 2555	cga Arg	agg Arg	cag Gln	Thr	gga Gly 2560	7680
cag Gln	gcc Ala	tat Tyr	Tyr	gta Val 2565	ata Ile	ctc Leu	ctc Leu	Asn	agg Arg 2570	ggc	cgt Arg	ctg Leu	Glu	gtg Val 2575	cat His	7728
ctc Leu	tcc Ser	Thr	999 Gly 2580	gca Ala	cga Arg	aca Thr	Met	agg Arg 2585	aaa Lys	att Ile	gtc Val	Ile	aga Arg 2590	çca Pro	gag Glu	7776
ccg Pro	Asn	ctg Leu 2595	ttt Phe	cat His	gat Asp	Gly	aga Arg 2600	gaa Glu	cat His	tcc Ser	Val	cat His 2605	gta Val	gag Glu	cga Arg	7824
Thr	aga Arg 2610	ggc Gly	atc Ile	ttt Phe	Thr	gtt Val 2615	caa Gln	gtg Val	gat Asp	Glu	aac Asn 2620	aga Arg	aga Arg	tac Tyr	atg Met	7872
caa Gln 2629	Asn	ctg Leu	aca Thr	Val	gaa Glu 2630	cag Gln	cct Pro	atc Ile	Glu	gtt Val 2635	aaa Lys	aag Lys	ctt Leu	Phe	gtt Val 2640	7920
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gac Asp	Phe	gca Ala 675	agg Arg	cct Pro	gtg Val	Ser	ttc Phe 680	aaa Lys	aat Asn	gct Ala	Asp	att Ile 685	ggt Gly	cgc Arg	tgt Cys	8064
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tgag	9 <b>9</b> 999	egt t	caac	ctgt	a to	catgo	cccaç	g cca	acta	aata	aaaa	ataaç	gtg (	taaco	ccagg	9324
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Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp Val Glu Tyr Lys Pro Trp 135 Gln Tyr His Ala Val Thr Asp Thr Glu Cys Leu Thr Leu Tyr Asn Ile Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala Lys Asp Asp Glu Val Ile 165 170 175 Cys Thr Ser Phe Tyr Ser Lys Ile His Pro Leu Glu Asn Gly Glu Ile His Ile Ser Leu Ile Asn Gly Arg Pro Ser Ala Asp Asp Pro Ser Pro 195 200 205 Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr Ile Arg Leu Arg Phe Gln 210 215 220 Arg Ile Arg Thr Leu Asn Ala Asp Leu Met Met Phe Ala His Lys Asp 225 230 235 240 Pro Arg Glu Ile Asp Pro Ile Val Thr Arg Arg Tyr Tyr Tyr Ser Val Lys Asp Ile Ser Val Gly Gly Met Cys Ile Cys Tyr Gly His Ala Arg 260 . 265 . 270Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys Ser Arg Cys Glu Cys Glu 275 280 285 His Asn Thr Cys Gly Asp Ser Cys Asp Gln Cys Cys Pro Gly Phe His 290 295 300 Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu Thr Lys Thr Glu Cys Glu Ala Cys Asn Cys His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp Glu Asn Val Ala Arg Arg Asn Leu Ser Leu Asn Ile Arg Gly Lys Tyr Ile Gly 340 345 350 Gly Gly Val Cys Ile Asn Cys Thr Gln Asn Thr Ala Gly Ile Asn Cys 355 360 365 Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro Lys Gly Val Ser Pro Asn 375 Tyr Pro Arg Pro Cys Gln Pro Cys His Cys Asp Pro Ile Gly Ser Leu 385 390 395 400 Asn Glu Val Cys Val Lys Asp Glu Lys His Ala Arg Arg Gly Leu Ala 405 410 415 Pro Gly Ser Cys His Cys Lys Thr Gly Phe Gly Gly Val Ser Cys Asp Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro Asp Cys Lys Ala Cys Asn 435 440 445

Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp Pro Cys Phe Gly Pro Cys Ile Cys Lys Glu Asn Val Glu Gly Gly Asp Cys Ser Arg Cys Lys Ser Gly Phe Phe Asn Leu Gln Glu Asp Asn Trp Lys Gly Cys Asp Glu Cys 485 490 495 Phe Cys Ser Gly Val Ser Asn Arg Cys Gln Ser Ser Tyr Trp Thr Tyr 500 505 510 Gly Lys Ile Gln Asp Met Ser Gly Trp Tyr Leu Thr Asp Leu Pro Gly 515 520 525 Arg Ile Arg Val Ala Pro Gln Gln Asp Asp Leu Asp Ser Pro Gln Gln Ile Ser Ile Ser Asn Ala Glu Ala Arg Gln Ala Leu Pro His Ser Tyr Tyr Trp Ser Ala Pro Ala Pro Tyr Leu Gly Asn Lys Leu Pro Ala Val 565 570 575 Gly Gly Gln Lcu Thr Phe Thr Ile Ser Tyr Asp Leu Glu Glu Glu Glu 585 Glu Asp Thr Glu Arg Val Leu Gln Leu Met Ile Ile Leu Glu Gly Asn 600 Asp Leu Ser Ile Ser Thr Ala Gln Asp Glu Val Tyr Leu His Pro Ser 610 615 620 615 Glu Glu His Thr Asn Val Leu Leu Leu Lys Glu Glu Ser Phe Thr Ile His Gly Thr His Phe Pro Val Arg Arg Lys Glu Phe Met Thr Val Leu 650 Ala Asn Leu Lys Arg Val Leu Leu Gln Ile Thr Tyr Ser Phe Gly Met Asp Ala Ile Phe Arg Leu Ser Ser Val Asn Leu Glu Ser Ala Val Ser Tyr Pro Thr Asp Gly Ser Ile Ala Ala Ala Val Glu Val Cys Gln Cys Pro Pro Gly Tyr Thr Gly Ser Ser Cys Glu Ser Cys Trp Pro Arg His 705 710 710 715 720 Arg Arg Val Asn Gly Thr Ile Phe Gly Gly Ile Cys Glu Pro Cys Gln 725 730 735Asn Cys Lys Asp His Thr Gly Gly Pro Tyr Cys Asp Lys Cys Leu Pro  $755 \hspace{1.5cm} 760 \hspace{1.5cm} 765$ Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr Ser Glu Asp Cys Gln Pro

770 775 780

Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn Asn Phe Ser Pro Thr Cys 785 790 795 800

His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Gly Cys Pro Val Gly 805 810 815

Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe Gly Gln  $\,\,$  820  $\,\,$  825  $\,\,$  830

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Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu Val Cys His Ser Gln Thr 900 905 910

Gly Gln Cys Glu Cys Arg Ala Asn Val Gln Gly Gln Arg Cys Asp Lys 915 920 925

Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser Ala Arg Gly Cys Val Pro 930 940

Cys Asn Cys Asn Ser Phe Gly Ser Lys Ser Phe Asp Cys Glu Glu Ser 945 950 955 960

Gly Gln Cys Trp Cys Gln Pro Gly Val Thr Gly Lys Lys Cys Asp Arg 965 970 975

Cys Ala His Gly Tyr Phe Asn Phe Gln Glu Gly Gly Cys Thr Ala Cys 980 985 990

Glu Cys Ser His Leu Gly Asn Asn Cys Asp Pro Lys Thr Gly Arg Cys 995 1000 1005

Ile Cys Pro Pro Asn Thr Ile Gly Glu Lys Cys Ser Lys Cys Ala Pro 1010 1015 1020

Asn Thr Trp Gly His Ser Ile Thr Thr Gly Cys Lys Ala Cys Asn Cys 1025 1030 1035 1040

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  1540 1545 1550
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- Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu Lys Val Ser Gln Ala Glu 1860 1865 1870
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2730

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2725

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					atc Ile 215											729
					ttc Phe											777
cag Gln	agg Arg	atc Ile	cgc Arg 245	acc Thr	ttg Leu	aat Asn	gca Ala	gac Asp 250	ttg Leu	atg Met	atg Met	ttt Phe	gct Ala 255	cac His	aaa Lys	825
					gat Asp											873
gtc Val	aag Lys 275	gat Asp	att Ile	tca Ser	gtt Val	ggc Gly 280	gly ggg	atg Met	tgc Cys	atc Ile	tgt Cys 285	tat Tyr	ggt Gly	cat His	gcc Ala	921
cgg Arg 290	gct Ala	tgt Cys	cca Pro	ctt Leu	gac Asp 295	cct Pro	gca Ala	aca Thr	aat Asn	aaa Lys 300	tca Ser	cgc Arg	tgt Cys	gag Glu	tgt Cys 305	969
gaa Glu	cat His	aac Asn	acc Thr	tgt Cys 310	999 Gly	gaa Glu	agc Ser	tgt Cys	gac Asp 315	agg Arg	tgc Cys	tgt Cys	cca Pro	gga Gly 320	ttc Phe	1017
				Trp	aga Arg									Glu		1065
gaa Glu	gca Ala	tgc Cys 340	aat Asn	tgt Cys	cac His	gga Gly	aaa Lys 345	gct Ala	gag Glu	gaa Glu	tgc Cys	tat Tyr 350	tat Tyr	gat Asp	gaa Glu	1113
act Thr	gtt Val 355	gct Ala	agc Ser	aga Arg	aat Asn	cta Leu 360	Ser	tta Leu	aat Asn	ata Ile	cat His 365	Gly	aag Lys	tac Tyr	atc Ile	1161
	Gly				atc Ile 375	Asn					Thr					1209

tgt Cys	gag Glu	aca Thr	tgt Cys	gtt Val 390	gat Asp	gga Gly	ttc Phe	ttc Phe	aga Arg 395	ccc Pro	aaa Lys	ggg Gly	gtg Val	tca Ser 400	cca Pro	1257
aat Asn	tat Tyr	cca Pro	aga Arg 405	cca Pro	tgc Cys	cag Gln	cca Pro	tgt Cys 410	cac His	tgt Cys	gat Asp	cca Pro	act Thr 415	ggc Gly	tcc Ser	1305
ctt Leu	agt Ser	gaa Glu 420	gtc Val	tgt Cys	gtc Val	aaa Lys	gat Asp 425	gag Glu	aaa Lys	tac Tyr	gcc Ala	cag Gln 430	cga Arg	999 Gly	ttg Leu	1353
aaa Lys	cct Pro 435	gga Gly	tcc Ser	tgt Cys	cac His	tgc Cys 440	aaa Lys	act Thr	ggc Gly	ttt Phe	gga Gly 445	ggc Gly	gtg Val	aac Asn	tgt Cys	1401
gat Asp 450	cgc Arg	tgt Cys	gtc Val	agg Arg	ggt Gly 455	tac Tyr	cat His	ggt Gly	tac Tyr	cca Pro 460	gac Asp	tgc Cys	caa Gln	ccc Pro	tgt Cys 465	1449
aac Asn	tgt Cys	agt Ser	ggc Gly	ttg Leu 470	ggg Gly	agc Ser	aca Thr	aat Asn	gag Glu 475	gac Asp	cct Pro	tgc Cys	gtt Val	999 Gly 480	ccc Pro	1497
tgt Cys	agc Ser	tgt Cys	aag Lys 485	gag Glu	aat Asn	gtt Val	gaa Glu	ggt Gly 490	gaa Glu	gac Asp	tgt Cys	agt Ser	cgt Arg 495	tgc Cys	aaa Lys	1545
	ggt Gly															1593
tgt Cys	ttc Phe 515	tgt Cysʻ	tca Ser	gga Gly	gta Val	tca Ser 520	aac Asn	aga Arg	tgt Cys	cag Gln	agt Ser 525	tcc Ser	tac Tyr	tgg Trp	acc Thr	1641
	glà 888															1689
ggc	cgc Arg	att Ile	cgg Arg	atg Met 550	gct Ala	ccc Pro	cag Gln	ctt Leu	gat Asp 555	aac Asn	cct Pro	gac Asp	tca Ser	cct Pro 560	cag Gln	1737
Gln	atc Ile	Ser	Ile 565	Ser	Asn	Ser	Glu	Ala 570	Arg	Lye	Ser	Leu	Leu 575	Asp	Gly	1785
tac Tyr	tac Tyr	tgg Trp 580	agt Ser	gca Ala	ccg Pro	cct Pro	cca Pro 585	tat Tyr	ctg Leu	gga Gly	aac Asn	aga Arg 590	ctt Leu	cca Pro	gct Ala	1833
gtt Val	999 Gly 595	gga Gly	cag Gln	ttg Leu	tca Ser	ttt Phe 600	acc Thr	atc Ile	tca Ser	tat Tyr	gac Asp 605	ctc Leu	gaa Glu	gaa Glu	gag Glu	1881
	gac Asp															1929
aat	gac	tta	aga	atc	agc	aca	gcg	tat	aag	gag	gtg	tac	tta	gag	cca	1977

Asn	Asp	Leu	Arg	Ile 630	Ser	Thr	Ala	Tyr	Lys 635	Glu	Val	Tyr	Leu	Glu 640	Pro	
	gaa Glu															2025
	cat His															2073
	aca Thr 675															2121
	gac Asp															2169
	tat Tyr															2217
	cca Pro															2265
cac His	cga Arg	aga Arg 740	gtt Val	aac Asn	ggc Gly	acc Thr	att Ile 745	ttt Phe	ggt Gly	ggc	att Ile	tgt Cys 750	gaa Glu	cca Pro	tgt Cys	2313
	tgc Cys 755															2361
ctg Leu 770	aac Asn	tgt Cys	aag Lys	gat Asp	cac His 775	aca Thr	ggt Gly	Gly 999	ccg Pro	tac Tyr 780	tgc Cys	aat Asn	gaa Glu	tgt Cys	ctc Leu 785	2409
cct Pro	gga Gly	ttc Phe	tat Tyr	ggt Gly 790	gat Asp	cct Pro	act Thr	cga Arg	gga Gly 795	agc Ser	cct Pro	gaa Glu	gac Asp	tgt Cys 800	cag Gln	2457
ccc Pro	tgt Cys	gcc Ala	tgt Cys 805	cca Pro	ctc Leu	aat Asn	atc Ile	cca Pro 810	tca Ser	aat Asn	aac Asn	ttt Phe	agt Ser 815	cca Pro	aca Thr	2505
	cat His															2553
	tac Tyr 835															2601
	cct			cct Pro						Pro					Asp	2649
					855					860					865	

				870					875					880		
tgt Cys	ctg Leu	att Ile	tgt Cys 885	aag Lys	cca Pro	ggt Gly	aca Thr	aca Thr 890	ggc Gly	cgg Arg	tac Tyr	tgt Cys	gag Glu 895	ctc Leu	tgt Cys	2745
Ala	Asp	900	Tyr	Pne	GIY	Asp	gcg Ala 905	Val	Asn	Thr	Lys	Asn 910	Cys	Gln	Pro	2793
Cys	Arg 915	Сув	Asp	Ile	Asn	Gly 920	tcc Ser	Phe	Ser	Glu	Asp 925	Cys	His	Thr	Arg	2841
act Thr 930	61À 888	caa Gln	tgt Cys	gag Glu	tgc Cys 935	aga Arg	ccc Pro	aat Asn	gtt Val	cag Gln 940	999 999	cgg Arg	cac His	tgt Cys	gac Asp 945	2889
GIu	Cys	Lys	Pro	Glu 950	Thr	Phe	ggc Gly	Leu	Gln 955	Leu	Gly	Arg	Gly	Суя 960	Leu	2937
ccc Pro	tgc Cys	aac Asn	tgc Cys 965	aat Asn	tct Ser	ttt Phe	ggg ggg	tct Ser 970	aag Lys	tcc Ser	ttt Phe	gac Asp	tgt Cys 975	gaa Glu	gca Ala	2985
agt Ser	<b>Gly</b> 999	cag Gln 980	tgc Cys	tgg Trp	tgc Cys	cag Gln	cct Pro 985	gga Gly	gta Val	gca Ala	ggg Gly	aag Lys 990	aaa Lys	tgt Cys	gac Asp	3033
cgt Arg	tgt Cys 995	gcc Ala	cat His	ggc Gly	Tyr	ttc Phe 1000	aac Asn	ttc Phe	caa Gln	Glu	gga Gly 1005	ggc Gly	tgc Cys	ata Ile	gct Ala	3081
	Asp			His			aac Asn		Cys					Gly		3129
tgc Cys	att Ile	tgc Cys	Pro	Pro	aat Asn	acc Thr	act Thr	Gly	gaa Glu 1035	aag Lys	tgt Cys	tct Ser	Glu	tgt Cys .040	ctt Leu	3177
ccc Pro	aac Asn	Thr	tgg Trp 1045	ggt Gly	cac His	agc Ser	att Ile	gtc Val 050	acc Thr	ggc Gly	tgt Cys	Lys	gtt Val .055	tgt Cys	aac Asn	3225
tgc Cys	Ser	act Thr .060	gtg Val	ggg Gly	tcc Ser	Leu	gct Ala 1065	tct Ser	cag Gln	tgc Cys	Asn	gta Val 070	aac Asn	acg Thr	ggc Gly	3273
GIn	tgc Cys .075	agc Ser	tgt Cys	cat His	Pro	aaa Lys .080	ttc Phe	tct Ser	ggt Gly	Met	aaa Lys 085	tgc Cys	tca Ser	gag Glu	tgc Cys	3321
agc Ser 1090	Arg	ggt Gly	cac His	Trp	aac Asn .095	tat Tyr	cct Pro	ctc Leu	Сув	act Thr 100	cta Leu	tgt Cys	gac Asp	Суз	ttc Phe 105	3369
ctt Leu	cca Pro	ggc Gly	Thr	gat Asp 110	gcc Ala	acg Thr	act Thr	ayD	gat Asp 115	ctg Leu	gag Glu	act Thr	Arg	aaa Lys 120	tgc Cys	3417

tcc tgt agt gat caa act gga cag tgc agc tgt aag gtg aat gtg gaa Ser Cys Ser Asp Gln Thr Gly Gln Cys Ser Cys Lys Val Asn Val Glu 1125 1130 1135	3465
ggc gtc cac tgt gac agg tgc cgg cct ggc aaa ttt gga cta gat gcc Gly Val His Cys Asp Arg Cys Arg Pro Gly Lys Phe Gly Leu Asp Ala 1140 1145 1150	3513
aag aac cca ctt ggc tgc agc agc tgc tac tgc ttt gga gtt act agt Lys Asn Pro Leu Gly Cys Ser Ser Cys Tyr Cys Phe Gly Val Thr Ser 1155 1160 1165	3561
Caa tgc tct gaa gca aag ggg ctg atc cgt acg tgg gtg act ttg agt Gln Cys Ser Glu Ala Lys Gly Leu Ile Arg Thr Trp Val Thr Leu Ser 1170 1175 1180 1185	3609
gat gaa cag acc att cta cct ctg gtg gat gag gcc ctg cag cac acg Asp Glu Gln Thr Ile Leu Pro Leu Val Asp Glu Ala Leu Gln His Thr 1190 1195 1200	3657
act acc aaa ggc att gct ttc cag aaa cca gag att gtt gca aag atg Thr Thr Lys Gly Ile Ala Phe Gln Lys Pro Glu Ile Val Ala Lys Met 1205 1210 1215	3705
gat gaa gtc agg caa gag ctc cat ttg gaa cct ttt tac tgg aaa ctc Asp Glu Val Arg Gln Glu Leu His Leu Glu Pro Phe Tyr Trp Lys Leu 1220 1225 1230	3753
cca caa caa ttt gaa ggg aaa aag ttg atg gct tat ggt ggc aaa ctc Pro Gln Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly Lys Leu 1235 1240 1245	3801
aag tat gcc atc tat ttt gag gct cgg gat gag aca ggc ttt gcc aca Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Asp Glu Thr Gly Phe Ala Thr 1250 1260 1265	3849
tat aaa cct caa gtt atc att cga ggt gga act cct act cat gct aga Tyr Lys Pro Gln Val Ile Ile Arg Gly Gly Thr Pro Thr His Ala Arg 1270 1275 1280	3897
att att acc aga cac atg gct gcc cct ctc att ggc cag ttg aca cgg Ile Ile Thr Arg His Met Ala Ala Pro Leu Ile Gly Gln Leu Thr Arg 1285 1290 1295	3945
cat gaa ata gaa atg aca gag aaa gaa tgg aaa tat tat ggt gat ga	3993
cct cga atc agt aga act gtg acc cgt gaa gac ttc ttg gat ata cta Pro Arg Ile Ser Arg Thr Val Thr Arg Glu Asp Phe Leu Asp Ile Leu 1315 1320 1325	4041
tat gat att cac tat atc ctt atc aag gct act tat gga aac gtt gtg Tyr Asp Ile His Tyr Ile Leu Ile Lys Ala Thr Tyr Gly Asn Val Val 1330 1335 1340 1345	4089
aga caa agc cgc att tct gaa atc tcc atg gaa gta gct gaa cca gga Arg Gln Ser Arg Ile Ser Glu Ile Ser Met Glu Val Ala Glu Pro Gly 1350 1355 1360	4137

HIS	Val	Leu	gca Ala 1365	Gly	Ser	Pro	Pro	Ala 1370	His	Leu	Ile	Glu :	Arg 1375	Cys	Asp	4185
Сув	Pro	Pro 1.380	ggc	Tyr	Ser	Gly	Leu 1385	Ser	Cys	Glu	Thr	Cys 1390	Ala	Pro	Gly	4233
Pne	tac Tyr 1395	cga Arg	ctt Leu	cgt Arg	Ser	gaa Glu 1400	cca Pro	ggt Gly	gjà aaa	Arg	act Thr 1405	cct Pro	gga Gly	cca Pro	acc Thr	4281
tta Leu 1410	Gly	acc Thr	tgt Cys	Val	ccc Pro 1415	tgc Cys	caa Gln	tgt Cys	Asn	gga Gly 1420	cac His	agc Ser	agt Ser	Gln	tgt Cys 1425	4329
gat Asp	cct Pro	gag Glu	acc Thr	tca Ser 1430	gta Val	tgc Cys	cag Gln	Asn	tgt Cys 1435	cag Gln	cat His	cac His	Thr	gct Ala 1440	ggt Gly	4377
gac Asp	ttc Phe	Сув	gag Glu 1445	cgc Arg	tgt Cys	gcc Ala	Leu	ggc Gly 1450	tac Tyr	tat Tyr	gga Gly	Ile	gtc Val 1455	agg Arg	gga Gly	4425
ttg Leu	Pro	aat Asn 1460	gac Asp	tgc Cys	caa Gln	Pro	tgt Cys .465	gct Ala	tgt Cys	cct Pro	Leu	att Ile 1470	tcg Ser	ccc Pro	agc Ser	4473
Asn	aat Asn 475	ttc Phe	agc Ser	ccc Pro	Ser	tgt Cys 1480	gta Val	ttg Leu	gaa Glu	Gly	ctg Leu 1485	gaa Glu	gat Asp	tac Tyr	cgt Arg	4521
tgc Cys 1490	Thr	gcc Ala	tgc Cys	Pro	agg Arg 1495	ggc Gly	tat Tyr	gaa Glu	Gly	cag Gln L500	tac Tyr	tgt Cys	gaa Glu	Arg	tgt Cys .505	4569
	,															
gcc Ala	cca	ggc Gly	tat Tyr 1	act Thr 510	ggc Gly	agc Ser	cca Pro	Ser	agc Ser .515	ccc	gga Gly	ggc Gly	Ser	tgc	caa Gln	4617
Ala gaa	cca Pro tgt	Gly gag Glu	Tyr	Thr 510 gac	Gly cct	Ser tat	Pro ggc Gly	Ser 1 tcc	Ser 515 cta	ccc Pro	Gly gtt	Gly ccc Pro	Ser tgt	tgc Cys 1520 gac	Gln cqq	4617 4665
Ala gaa Glu gtc	cca Pro tgt Cys aca Thr	gag Glu gga	Tyr 1 tgt Cys	Thr 1510 gac Asp	Gly cct Pro	Ser tat Tyr tgc Cys	ggc Gly cgc	ser tcc ser .530	Ser 515 cta Leu	ccc Pro ecg Pro	Gly gtt Val aca Thr	Gly ccc Pro	tgt Cys 1535 agg	tgc Cys 1520 gac Asp	Gln cgg Arg	
gaa Glu gtc Val gat Asp	cca Pro tgt Cys aca Thr	gag Glu gga Gly .540	tgt Cys 1525	Thr 510 gac Asp tgc Cys	Gly cct Pro acg Thr tgg Trp	tat Tyr tgc Cys	ggc Gly cgc Arg 545	Ser 1 tcc Ser .530 cct Pro	Ser 515 cta Leu gga Gly	ccc Pro ccg Pro gcc Ala	Gly gtt Val aca Thr	CCC Pro gga Gly .550	tgt Cys 1535 agg Arg	tgc Cys 520 gac Asp aag Lys	Gln cgg Arg tgt Cys	4665
Ala gaa Glu gtc Val gat Asp	cca Pro tgt Cys aca Thr 1 ggc Gly 555 gga Gly	gag Glu gga Gly 540 tgc Cys	tgt Cys 1525 ctc Leu	Thr 510 gac Asp tgc Cys cac His	Gly cct Pro acg Thr tgg Trp	tat Tyr tgc Cys cat His 560	ggc Gly cgc Arg .545 gca Ala	tcc Ser .530 cct Pro cgc Arg	Ser .515 cta Leu gga Gly gag Glu ctt Leu	ccc Pro ccg Pro gcc Ala ggt Gly	gtt Val aca Thr gca Ala 565	Gly ccc Pro gga Gly 550 gag Glu ctg	tgt Cys 535 agg Arg tgt Cys	tgc Cys 1520 gac Asp aag Lys gtc Val	cgg Arg tgt Cys ttt Phe	4665 4713
Ala  gaa Glu  gtc Val  gat Asp  tgt Cys 1570 gag	cca Pro tgt Cys aca Thr 1 ggc Gly 555 gga Gly	gag Glu 1 gga Gly 540 tgc Cys	Tyr  tgt Cys L525 ctc Leu gag Glu gag Glu acc Thr	Thr .510 gac Asp tgc Cys cac His tgt Cys	Gly cct Pro acg Thr tgg Trp laca Thr 575	tat Tyr tgc Cys 1 cat His 560 ggc Gly	Pro ggc Gly 1 cgc Arg 545 gca Ala ctt Leu	Ser 1 tcc Ser .530 cct Pro cgc Arg ctt Leu ctc Leu	Ser 515 cta Leu gga Gly gag Glu ctt Leu lacq	ccc Pro	gtt Val aca Thr 1 gca Ala 565 gac Asp	Gly ccc Pro gga Gly 550 gag Glu ctg Leu	tgt Cys .535 agg Arg tgt Cys gct Ala	tgc Cys 520 gac Asp aag Lys gtc Val	cgg Arg tgt Cys ttt Phe cta Leu 585	4665 4713 4761

Tyr Lys	Ile Leu 1605	Tyr Gly		Asn Thi 1610	r Thr Gln	Glu Leu 1615	Lys His	
Leu Leu	tca ccg Ser Pro 620	caa cgg Gln Arg	gca cca Ala Pro 1625	gag agg Glu Arg	g ctc att g Leu Ile	cag ttg Gln Leu 1630	gca gag Ala Glu	4953
		Thr Leu			a aat gag r Asn Glu 1645			5001
			Asp Gly		a aca gga n Thr Gly 1660			5049
	Asn Ser				a gaa ttc u Glu Phe 5	Ile Lys		5097
			Ile Asn		a gct gta s Ala Val			5145
Thr Leu					g aga aac u Arg Asn			5193
		Asp Arg			a ctg aga u Leu Arg 1725			5241
caa aca Gln Thr 1730	cag aag Gln Lys	gaa gtt Glu Val 1735	Ala Glu	gat gag Asp Gl	g ctc gtg u Leu Val 1740	gca gca Ala Ala	gaa ggc Glu Gly 1745	5289
ctt cta								
	Lys Arg				a gag ccc y Glu Pro 5	Arg Ala		5337
Leu Leu	Lys Arg	Val Asn 1750 aag gat	Lys Leu ctc cag Leu Gln	Phe Gly 1759 cag aa	y Glu Pro	Arg Ala	Gln Asn 1760 aag aac	5337 5385
gaa gat Glu Asp	Lys Arg atg gaa Met Glu 1765 gat gat	Val Asn 1750 aag gat Lys Asp gct tgg	ctc cag Leu Gln	Phe Gly 1759 cag aa Gln Lys 1770 ttg ag	y Glu Pro  a ctg gca s Leu Ala  a gaa gcc g Glu Ala	gag tac Glu Tyr 1775	Gln Asn 1760 aag aac Lys Asn	
gaa gat Glu Asp aaa ctt Lys Leu 1 cga gat	atg gaa Met Glu 1765 gat gat Asp Asp 780 gct aat	Val Asn 1750 aag gat Lys Asp gct tgg Ala Trp cgt ttg Arg Leu	ctc cag Leu Gln gat cta Asp Leu 1785	cag aa. Gln Ly 1770  ttg ag. Leu Ar	y Glu Pro  a ctg gca s Leu Ala  a gaa gcc g Glu Ala	gag tac Glu Tyr 1775 act gat Thr Asp 1790 aac atg Asn Met	Gln Asn 1760 aag aac Lys Asn aaa acc Lys Thr	5385
gaa gat Glu Asp aaa ctt Lys Leu 1 cga gat Arg Asp 1795 ctg gag	atg gaa Met Glu 1765 gat gat Asp Asp 780 gct aat Ala Asn	Val Asn 1750 aag gat Lys Asp gct tgg Ala Trp cgt ttg Arg Leu	ctc cag Leu Gln gat cta Asp Leu 1785 tct gct Ser Ala 1800 gct att Ala Ile	Phe Gl; 175: cag aaa Gln Ly: 1770 ttg ag. Leu Ar; gcc aa Ala As:	y Glu Pro  a ctg gca s Leu Ala a gaa gcc g Glu Ala t caa aaa n Gln Lys	gag tac Glu Tyr 1775 act gat Thr Asp 1790 aac atg Asn Met	Gln Asn 1760  aag aac Lys Asn  aaa acc Lys Thr  acc ata Thr Ile  ata gag	5385 5433
gaa gat Glu Asp laaa ctt Lys Leu la cga gat Arg Asp 1795 ctg gag Leu Glu 1810 aac act	atg gaa Met Glu 1765 gat gat Asp Asp 780 gct aat Ala Asn aca aag Thr Lys	Val Asn 1750  aag gat Lys Asp  gct tgg Ala Trp  cgt ttg Arg Leu  aag gag Lys Glu 1815 gaa ggc	ctc cag Leu Gln gat cta Asp Leu 1785 tct gct Ser Ala 1800 gct att Ala Ile	Phe Gly 175:  cag aaa Gln Ly: 1770  ttg ag. Leu Ar.  gcc aaa Ala As: gaa gg Glu Gly  atc ct	y Glu Pro  a ctg gca s Leu Ala  a gaa gcc g Glu Ala  t caa aaa n Gln Lys 1805  t agc aaa y Ser Lys 1820  t gat gaa u Asp Glu	gag tac Glu Tyr 1775 act gat Thr Asp 1790 aac atg Asn Met cga caa Arg Gln gcc aat Ala Asn	Gln Asn 1760  aag aac Lys Asn  aaa acc Lys Thr  acc ata Thr Ile  ata gag Ile Glu 1825 caa ctc	5385 5433 5481

1845		1850	1855	
aag ttg cca cca Lys Leu Pro Pro 1860	Met Ser Glu	gag ctg agt Glu Leu Ser 865	gac aaa ata gat ga Asp Lys Ile Asp As 1870	c ctc 5673 p Leu
gcc cag gaa ata Ala Gln Glu Ile 1875	aag gac aga Lys Asp Arg 1880	agg ctt gct Arg Leu Ala	gag aag gtg ttc ca Glu Lys Val Phe Gl 1885	g gct 5721 n Ala
gag agc cat gct Glu Ser His Ala 1890	gct cag ctg Ala Gln Leu 1895	aac gac tcg Asn Asp Ser	tot got gta ott ga Ser Ala Val Leu As 1900	t gga 5769 p Gly 1905
Ile Leu Asp Glu	gct aag aac Ala Lys Asn 1910	atc tct ttc Ile Ser Phe 1915	aat gcc acg gca gc Asn Ala Thr Ala Al 192	a Phe
aga gct tac agt Arg Ala Tyr Ser 1925	Asn Ile Lys .	gac tac att Asp Tyr Ile 1930	gat gaa gct gag aa. Asp Glu Ala Glu Ly 1935	a gtg 5865 s Val
gcc aga gaa gcc Ala Arg Glu Ala 1940	Lys Glu Leu .	gcc caa ggg Ala Gln Gly 945	gct aca aaa ctg gc Ala Thr Lys Leu Al 1950	a aca 5913 a Thr
agt cct cag ggc Ser Pro Gln Gly 1955	tta tta aaa Leu Leu Lys 1960	gaa gat gcc Glu Asp Ala	aaa ggc tcc ctt ca Lys Gly Ser Leu Gl 1965	g aaa 5961 n Lys
		Ala Lys Lys	cta gca aac gat gt Leu Ala Asn Asp Va 1980	
Gly Asn His Asn	gat cta aat o Asp Leu Asn . 1990	gac ctg aaa Asp Leu Lys 1995	acc agg tta gaa ac Thr Arg Leu Glu Th 200	r Ala
gac ctt aga aac Asp Leu Arg Asn 2005	agt gga ctt   Ser Gly Leu	cta gga gct Leu Gly Ala 2010	cta aat gac acc at Leu Asn Asp Thr Met 2015	g gac 6105 Asp
	Ile Thr Asn		gct aaa ctg cag gcd Ala Lys Leu Gln Ala 2030	
aaa gag aaa gcc Lys Glu Lys Ala 2035	aga gaa gcc a Arg Glu Ala a 2040	aat gac aca Asn Asp Thr	gca aaa gct gtc ctg Ala Lys Ala Val Let 2045	ggcc 6201 ıAla
		Asn Leu Asp	ggc ctg aag caa aad Gly Leu Lys Gln Asi 2060	
Asn Lys Leu Ala	gac agc gtg o Asp Ser Val i 2070	gcc aaa acg Ala Lys Thr 2075	aac gct gtg gtg aaa Asn Ala Val Val Lys 2080	Asp
			ggc act tcc gtg aga Gly Thr Ser Val Arc 2095	

			gac aaa ctc Asp Lys Leu 2		
	Asp Asn Leu		att tct gaa Ile Ser Glu 2125		
			tct atc aaa Ser Ile Lys 2140	Val Ser Val	
		Arg Thr Tyr	agg cca gaa Arg Pro Glu 2155		
Ser Tyr Asn	aac atc gtt Asn Ile Val 2165	gtc cat gtc Val His Val 2170	aag acc gct Lys Thr Ala	gtt gcc gac Val Ala Asp 2175	aac 6585 Asn
ctc ctt ttt Leu Leu Phe 2180	tat ctt gga Tyr Leu Gly	agt gcc aaa Ser Ala Lys 2185	ttt att gac Phe Ile Asp	ttt ctt gct Phe Leu Ala 190	ata 6633 Ile
gaa atg cgc Glu Met Arg 2195	Lys Gly Lys	gtc agc ttc Val Ser Phe 2200	ctc tgg att Leu Trp Ile 2205	gtt ggc tct Val Gly Ser	gga 6681 Gly
gtt ggc cga Val Gly Arg 2210	gta ggg ttt Val Gly Phe 2215	Pro Asp Leu	g acc atc gac n Thr Ile Asp 2220	Asp Ser Tyr	tgg 6729 Trp 2225
tac cgt att Tyr Arg Ile	gaa gca tca Glu Ala Ser 2230	aga acg gga Arg Thr Gly	aga aat gga Arg Asn Gly 2235	tct att tct Ser Ile Ser 2240	gtg 6777 Val
Arg Ala Leu	gat gga ccc Asp Gly Pro 2245	aaa gcc agt Lys Ala Sei 2250	atg gta ccc Met Val Pro	agc acc tac Ser Thr Tyr 2255	cat 6825 His
tca gtg tct Ser Val Ser 2260	Pro Pro Gly	tat act ato Tyr Thr Ilo 2265	c cta gat gtg e Leu Asp Val	gat gca aat Asp Ala Asn 2270	gca 6873 Ala
atg ctg ttt Met Leu Phe 2275	gtt ggt ggo Val Gly Gly	ctg acc gga Leu Thr Gly 2280	a aaa ata aag y Lys Ile Lys 2285	aag gcc gat Lys Ala Asp	gct 6921 Ala
gta cgt gtg Val Arg Val 2290	atc acc tto Ile Thr Phe 2295	Thr Gly Cy	t atg gga gaa s Met Gly Glu 2300	Thr Tyr Phe	gac 6969 Asp 2305
			e cgg gag aaa e Arg Glu Lys 2315		
Lys Gly Cys	act gtc ago Thr Val Ser 2325	c cca caa gt r Pro Gln Va 233	g gaa gat agt 1 Glu Asp Ser 0	gag ggg act Glu Gly Thr 2335	att 7065, Ile

cag Gln	ttt Phe	gat Asp	ggt Gly	gaa Glu	ggc Gly	tat Tyr	gca Ala	tta Leu	gtg Val	agc Ser	egg Arg	ccc Pro	atc Ile	cgc Ara	tgg Trp	7113
	2	340				2	345					350			•	
Tyr	ccc Pro 355	aac Asn	atc Ile	tcc Ser	Thr	gtc Val 2360	atg Met	ttc Phe	aag Lys	Phe	cgg Arg 365	aca Thr	ttt Phe	tca Ser	tca Ser	7161
agt Ser 2370	Ala	ctc Leu	ctg Leu	Met	tat Tyr 375	ctt Leu	gcc Ala	aca Thr	Arg	gac Asp 380	ctg Leu	aaa Lys	gat Asp	Phe	atg Met 2385	7209
agt Ser	gta Val	gag Glu	Leu	agt Ser 390	gat Asp	gga Gly	cat His	۷al	aaa Lys 395	gtc Val	agc Ser	tat Tyr	Asp	ctg Leu 2400	ggc Gly	7257
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	Lys	gca Ala 420				Ser					Gln					7353
Ile		gac Asp			Ser					Asn						7401
	Gly	aac Asn		Phe					Lys					Ile		7449
		ggc Gly	Leu					Asn					Āla			7497
gaa Glu	gtc Val	aat Asn 2	gtg Val 485	aag Lys	aaa Lys	tac Tyr	Ser	ggc Gly 490	tgc Cys	ctc Leu	aaa Lys	Asp	att Ile 495	gaa Glu	att Ile	7545
	Arg	aca Thr 500				Ile					Asp					7593
Thr		ggc Gly			Leu					Thr						7641
cct Pro 2530	Gly	ttt Phe	gtg Val	Glu	ctt Leu 535	gcc Ala	gct Ala	gtg Val	Ser	att Ile 540	gat Asp	gtt Val	gga Gly	Thr	gaa Glu 2545	7689
		ctg Leu	Ser					Asn					Ile			7737
		gga Gly 2					Pro					Arg				7785
aca	cag	gct	tat	tat	gcc	ata	ttc	ctc	aac	aag	ggc	cgc	ttg	gaa	gtg	7833

Thr	Gln 2	Ala 580	Tyr	Tyr	Ala		Phe 585	Leu	Asn	Lys		Arg 2590	Leu	Glu	Val	
His					Thr					Lys				aaa Lys		7881
	Pro			Phe					Glu					gta Val 2		7929
			Gly					Gln					Arg	aga Arg 2640		7977
atc Ile	caa Gln	Asn	ctg Leu 2645	aca Thr	gag Glu	gaa Glu	Gln	Pro 2650	atc Ile	gaa Glu	gtg Val	Lys	aag Lys :655	ctc Leu	ttt Phe	8025
	Gly					Glu					Pro			aat Asn		8073
Pro	gcc Ala 1675	ttt Phe	caa Gln	ggc Gly	Суз	gtg Val 2680	tgg Trp	aac Asn	ctt Leu	Val	att Ile 2685	aac Asn	tcc Ser	atc Ile	ccc Pro	8121
atg Met 2690	Asp	ttt Phe	gcg Ala	Gln	cct Pro 2695	ata Ile	gcc Ala	ttc Phe	Lys	aat Asn 2700	gcc Ala	gac Asp	att Ile	ggt Gly 2	cgc Arg 2705	8169
tgt Cys	acc Thr	tat Tyr	Gln	aag Lys 2710	ccc Pro	cgg Arg	gaa Glu	Asp	gag Glu 2715	agt Ser	gaa Glu	gca Ala	Val	cca Pro 2720	gct Ala	8217
gaa Glu	gtt Val	Ile	gtc Val 2725	cag Gln	cct Pro	cag Gln	Ser	gtg Val 2730	ccc Pro	acc Thr	cct Pro	Ala	ttc Phe 2735	cct Pro	ttc Phe	8265
	Val					His					Ala			gaa Glu		8313
Ala	ctt Leu 2755	ctg Leu	aca Thr	ggg Gly	Ser	aag Lys 2760	Gln	ttt Phe	Gly 999	Leu	tcc Ser 2765	aga Arg	aac Asn	agc Ser	cac His	8361
Ile 2770	Ala )	Ile	Val	Phe	Asp 2775	Asp	Thr	Lys	Val	Lys 2780	Asn	Arg	Leu		Ile 2785	8409
gag Glu	ctg Leu	gag Glu	Val	cga Arg 2790	act Thr	gaa Glu	gct Ala	Glu	tca Ser 2795	Gly	ttg Leu	ctc Leu	Phe	tac Tyr 2800	atg Met	8457
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														acc Thr		8553

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3035

9225

9273

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Val Asp Ala Gln Ser Pro Asn Ser Ala Ser Thr Ser Ala Asp Thr Asn

Asp Pro Val Phe Val Gly Gly Phe Pro Gly Gly Leu Asn Gln Phe Gly 3065

3050 gac cct gtt ttc gtt ggc ggt ttc cca ggt ggc ctc aat cag ttt ggc

3045

9321

9369

9422

ctg acc acc aac att agg ttc cga ggc tgc atc cga tct ctg aag ctc Leu Thr Thr Asn Ile Arg Phe Arg Gly Cys Ile Arg Ser Leu Lys Leu 3075 3085 acc aaa ggc act gca aac cgc tgg agg tta att ttg cca agg ccc tgg Thr Lys Gly Thr Ala Asn Arg Trp Arg Leu Ile Leu Pro Arg Pro Trp 3095 3100 aac tgaggggtgt tcaacctgta tcatgcccga ctacctaata aagatagttc Asn aatcctgagg agaattcatc aaaacaagta tatcaagtta aacaatatac actcctatca 9482 tattaataaa actaatgtgc ageggeege <210> 10 <211> 3106 <212> PRT <213> Mus musculus Met Pro Ala Ala Thr Ala Gly Ile Leu Leu Leu Leu Leu Leu Gly Thr Leu Glu Gly Ser Gln Thr Gln Arg Arg Gln Ser Gln Ala His Gln Gln 20 25 30Arg Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser Asn Ala Leu Ile 35 40 45 Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys Lys 50 60Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys Arg 65 70 75 80 Ile Cys Asn Gln Asn Ser Ser Asn Pro Tyr Gln Arg His Pro Ile Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile Lys 105 Asn Gly Val Glu Tyr His Tyr Val Thr Ile Thr Leu Asp Leu Gln Gln 120 Val Phe Gln Ile Ala Tyr Val Ile Val Lys Ala Ala Asn Ser Pro Arg Pro Gly Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp Val Glu Tyr Lys 150 155 Pro Trp Gln Tyr His Ala Val Thr Asp Thr Glu Cys Leu Thr Leu Tyr Asn Ile Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala Lys Asp Asp Glu 185 Val Ile Cys Thr Ser Phe Tyr Ser Lys Ile His Pro Leu Glu Asn Gly

Glu Ile His Ile Ser Leu Ile Asn Gly Arg Pro Ser Ala Asp Asp Pro Ser Pro Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr Ile Arg Leu Arg Phe Gln Arg Ile Arg Thr Leu Asn Ala Asp Leu Met Met Phe Ala His 250 Lys Asp Pro Arg Glu Ile Asp Pro Ile Val Thr Arg Arg Tyr Tyr Tyr 260 265 270 Ser Val Lys Asp Ile Ser Val Gly Gly Met Cys Ile Cys Tyr Gly His 275 280 285 Ala Arg Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys Ser Arg Cys Glu Cys Glu His Asn Thr Cys Gly Glu Ser Cys Asp Arg Cys Cys Pro Gly 305 310 315 320 Phe His Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu Thr Lys Ser Glu 325 330 335Cys Glu Ala Cys Asn Cys His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp \$340\$ \$345 \$350Glu Thr Val Ala Ser Arg Asn Leu Ser Leu Asn Ile His Gly Lys Tyr Ile Gly Gly Gly Val Cys Ile Asn Cys Thr His Asn Thr Ala Gly Ile 370 375 380 Asn Cys Glu Thr Cys Val Asp Gly Phe Phe Arg Pro Lys Gly Val Ser 385 390 395 400 Pro Asn Tyr Pro Arg Pro Cys Gln Pro Cys His Cys Asp Pro Thr Gly Ser Leu Ser Glu Val Cys Val Lys Asp Glu Lys Tyr Ala Gln Arg Gly
420 425 430 Leu Lys Pro Gly Ser Cys His Cys Lys Thr Gly Phe Gly Gly Val Asn 435 440 445 Cys Asp Arg Cys Val Arg Gly Tyr His Gly Tyr Pro Asp Cys Gln Pro 450 450 460 Cys Asn Cys Ser Gly Leu Gly Ser Thr Asn Glu Asp Pro Cys Val Gly Pro Cys Ser Cys Lys Glu Asn Val Glu Gly Glu Asp Cys Ser Arg Cys Lys Ser Gly Phe Phe Asn Leu Gln Glu Asp Asn Gln Lys Gly Cys Glu 505 Glu Cys Phe Cys Ser Gly Val Ser Asn Arg Cys Gln Ser Ser Tyr Trp

520

Thr Tyr Gly Asn Ile Gln Asp Met Arg Gly Trp Tyr Leu Thr Asp Leu Ser Gly Arg Ile Arg Met Ala Pro Gln Leu Asp Asn Pro Asp Ser Pro 545 550 555 560 Gln Gln Ile Ser Ile Ser Asn Ser Glu Ala Arg Lys Ser Leu Leu Asp 565 570 575 Gly Tyr Tyr Trp Ser Ala Pro Pro Pro Tyr Leu Gly Asn Arg Leu Pro 585 Ala Val Gly Gly Gln Leu Ser Phe Thr Ile Ser Tyr Asp Leu Glu Glu Glu Glu Asp Asp Thr Glu Lys Leu Leu Gln Leu Met 1le Ile Phe Glu Gly Asn Asp Leu Arg Ile Ser Thr Ala Tyr Lys Glu Val Tyr Leu Glu 625 630 635 640 Pro Ser Glu Glu His Val Glu Glu Val Ser Leu Lys Glu Glu Ala Phe 645 650 655 Thr Ile His Gly Thr Asn Leu Pro Val Thr Arg Lys Asp Phe Met Ile 660  $\phantom{0}665$   $\phantom{0}670$ Val Leu Thr Asn Leu Gly Glu Ile Leu Ile Gln Ile Thr Tyr Asn Leu 675 680 685 Gly Met Asp Ala Ile Phe Arg Leu Ser Ser Val Asn Leu Glu Ser Pro Val Pro Tyr Pro Thr Asp Arg Arg Ile Ala Thr Asp Val Glu Val Cys 705 710 715 . 720 Gln Cys Pro Pro Gly Tyr Ser Gly Ser Ser Cys Glu Thr Cys Trp Pro Arg His Arg Arg Val Asn Gly Thr Ile Phe Gly Gly Ile Cys Glu Pro 740  $\phantom{000}745$   $\phantom{000}750$ Cys Gln Cys Phe Ala His Ala Glu Ala Cys Asp Asp Ile Thr Gly Glu Cys Leu Asn Cys Lys Asp His Thr Gly Gly Pro Tyr Cys Asn Glu Cys 770 780 Leu Pro Gly Phe Tyr Gly Asp Pro Thr Arg Gly Ser Pro Glu Asp Cys 785 790 795 800 Gln Pro Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn Asn Phe Ser Pro 805 810 815 Thr Cys His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Glu Cys Pro 820 \$825\$Ile Gly Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe 835 840 845Gly Gln Pro Ser Val Pro Gly Gly Ser Cys Gln Pro Cys Gln Cys Asn

850 855 860

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- Cys Ala Asp Gly Tyr Phe Gly Asp Ala Val Asn Thr Lys Asn Cys Gln 900 905 910
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- Asp Arg Cys Ala His Gly Tyr Phe Asn Phe Gln Glu Gly Gly Cys Ile 995 1000 1005
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- Leu Pro Asn Thr Trp Gly His Ser Ile Val Thr Gly Cys Lys Val Cys 1045 1050 1055
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Ser Asp Glu Gln Thr Ile Leu Pro Leu Val Asp Glu Ala Leu Gln His 185 1190 1195 1200

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- Met Asp Glu Val Arg Gln Glu Leu His Leu Glu Pro Phe Tyr Trp Lys 1220 1225 1230
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- Leu Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Asp Glu Thr Gly Phe Ala 1250 1255 1260
- Thr Tyr Lys Pro Gln Val Ile Ile Arg Gly Gly Thr Pro Thr His Ala 265 1270 1275 1280
- Arg Ile Ile Thr Arg His Met Ala Ala Pro Leu Ile Gly Gln Leu Thr 1285 1290 1295
- Arg His Glu Ile Glu Met Thr Glu Lys Glu Trp Lys Tyr Tyr Gly Asp 1300 1305 1310
- Asp Pro Arg Ile Ser Arg Thr Val Thr Arg Glu Asp Phe Leu Asp Ile 1315 1320 1325
- Leu Tyr Asp Ile His Tyr Ile Leu Ile Lys Ala Thr Tyr Gly Asn Val 1330 1335 1340
- Val Arg Gln Ser Arg Ile Ser Glu Ile Ser Met Glu Val Ala Glu Pro 345 1350 1355 1360
- Gly His Val Leu Ala Gly Ser Pro Pro Ala His Leu Ile Glu Arg Cys 1365 1370 1375
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- Ser Asn Asn Phe Ser Pro Ser Cys Val Leu Glu Gly Leu Glu Asp Tyr 1475 1480 1485
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Cys Ala Pro Gly Tyr Thr Gly Ser Pro Ser Ser Pro Gly Gly Ser Cys 505 1510 1515 1520

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- Arg Val Thr Gly Leu Cys Thr Cys Arg Pro Gly Ala Thr Gly Arg Lys 1540 1545 1550
- Cys Asp Gly Cys Glu His Trp His Ala Arg Gl $\hat{u}$  Gly Ala Glu Cys Val 1555 1560 1565
- Phe Cys Gly Asp Glu Cys Thr Gly Leu Leu Leu Gly Asp Leu Ala Arg 1570 1575 1580
- Leu Glu Gln Met Thr Met Asn Ile Asn Leu Thr Gly Pro Leu Pro Ala 585 1590 1595 1600
- Pro Tyr Lys Ile Leu Tyr Gly Leu Glu Asn Thr Thr Glu Glu Leu Lys 1605 1610 . 1615
- His Leu Leu Ser Pro Gln Arg Ala Pro Glu Arg Leu Ile Gln Leu Ala 1620 1625 1630
- Glu Gly Asn Val Asn Thr Leu Val Met Glu Thr Asn Glu Leu Leu Thr 1635 1640 1645
- Arg Ala Thr Lys Val Thr Ala Asp Gly Glu Gln Thr Gly Gln Asp Ala 1650 1655 1660
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- Leu Gln Lys Glu Ile Asp Arg Met Leu Lys Glu Leu Arg Ser Lys Asp 1715 1720 1725
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- Asn Lys Leu Asp Asp Ala Trp Asp Leu Leu Arg Glu Ala Thr Asp Lys 1780 1785 1790
- Thr Arg Asp Ala Asn Arg Leu Ser Ala Ala Asn Gln Lys Asn Met Thr 1795 1800 1805
- Ile Leu Glu Thr Lys Lys Glu Ala Ile Glu Gly Ser Lys Arg Gln Ile 1810 1815 1820
- Glu Asn Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp Glu Ala Asn Gln

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- Leu Leu Gly Glu Ile Asn Ser Val Ile Asp Tyr Val Asp Asp Ile Lys 1845 1850 1855
- Thr Lys Leu Pro Pro Met Ser Glu Glu Leu Ser Asp Lys Ile Asp Asp 1860 1865 1870
- Leu Ala Gln Glu Ile Lys Asp Arg Arg Leu Ala Glu Lys Val Phe Gln 1875 1880 1885
- Ala Glu Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu Asp 1890 1895 1900
- Gly Ile Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala 905 1910 1915 1920
- Phe Arg Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys 1925 1930 1935
- Val Ala Arg Glu Ala Lys Glu Leu Ala Cln Gly Ala Thr Lys Leu Ala 1940 1945 1950
- Thr Ser Pro Gln Gly Leu Leu Lys Glu Asp Ala Lys Gly Ser Leu Gln 1955 1960 1965
- Lys Ser Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu Ala Asn Asp Val . 1970 1975 1980
- Lys Gly Asn His Asn Asp Leu Asn Asp Leu Lys Thr Arg Leu Glu Thr 985 1990 1995 2000
- Ala Asp Leu Arg Asn Ser Gly Leu Leu Gly Ala Leu Asn Asp Thr Met 2005 2010 2015
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- Val Lys Glu Lys Ala Arg Glu Ala Asn Asp Thr Ala Lys Ala Val Leu 2035 2040 2045
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- Asp Pro Ser Lys Asn Lys Ile Ile Ala Asp Ala Gly Thr Ser Val Arg 2085 2090 2095
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- Lys Glu Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser Glu Ile Lys Glu 2115 2120 2125
- Leu Ile Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile Lys Val Ser Val 2130 2135 2140
- Ser Ser Gly Gly Asp Cys Val Arg Thr Tyr Arg Pro Glu Ile Lys Lys 145 2150 2155 2160

Gly Ser Tyr Asn Asn Ile Val Val His Val Lys Thr Ala Val Ala Asp 2165 2170 2175

- Asn Leu Leu Phe Tyr Leu Gly Ser Ala Lys Phe Ile Asp Phe Leu Ala
- Ile Glu Met Arg Lys Gly Lys Val Ser Phe Leu Trp Ile Val Gly Ser 2195 2200 2205
- Gly Val Gly Arg Val Gly Phe Pro Asp Leu Thr Ile Asp Asp Ser Tyr 2210 2215 2220
- Trp Tyr Arg Ile Glu Ala Ser Arg Thr Gly Arg Asn Gly Ser Ile Ser 225 2230 2235 2240
- Val Arg Ala Leu Asp Gly Pro Lys Ala Ser Met Val Pro Ser Thr Tyr 2245 2250 2255
- His Ser Val Ser Pro Pro Gly Tyr Thr Ile Leu Asp Val Asp Ala Asn 2260 2265 2270
- Ala Met Leu Phe Val Gly Gly Leu Thr Gly Lys Ile Lys Lys Ala Asp 2275 2280 2285
- Ala Val Arg Val Ile Thr Phe Thr Gly Cys Met Gly Glu Thr Tyr Phe 2290 2295 2300
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- Cys Lys Gly Cys Thr Val Ser Pro Gln Val Glu Asp Ser Glu Gly Thr 2325 2330 2335
- Ile Gln Phe Asp Gly Glu Gly Tyr Ala Leu Val Ser Arg Pro Ile Arg 2340 2345 2350
- Trp Tyr Pro Asn Ile Ser Thr Val Met Phe Lys Phe Arg Thr Phe Ser 2355 2360 2365
- Ser Ser Ala Leu Leu Met Tyr Leu Ala Thr Arg Asp Leu Lys Asp Phe 2370 2375 2380
- Met Ser Val Glu Leu Ser Asp Gly His Val Lys Val Ser Tyr Asp Leu 385 2390 2395 2400
- Gly Ser Gly Met Thr Ser Val Val Ser Asn Gln Asn His Asn Asp Gly 2405 2410 2415
- Lys Trp Lys Ala Phe Thr Leu Ser Arg Ile Gln Lys Gln Ala Asn Ile \$2420\$ \$2425\$ \$2430
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- Ser Ser Gly Asn Asn Phe Gly Leu Asp Leu Lys Ala Asp Asp Lys Ile 2450 2455 2460
- Tyr Phe Gly Gly Leu Pro Thr Leu Arg Asn Leu Ser Met Lys Ala Arg 465 2470 2475 2480

Pro Glu Val Asn Val Lys Lys Tyr Ser Gly Cys Leu Lys Asp Ile Glu 2485 2490 2495

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- Thr Ala Lys Lys Ile Lys Asn Arg Leu Glu Leu Val Val Asp Gly Asn 025 3030 3035 3040
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- Asn Asp Pro Val Phe Val Gly Gly Phe Pro Gly Gly Leu Asn Gln Phe 3060 3065 3070
- Gly Leu Thr Thr Asn Ile Arg Phe Arg Gly Cys Ile Arg Ser Leu Lys 3075 3080 3085
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			gga Gly													144
			gtg Val													192
			tac Tyr													240
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			att Ile 100													336
			aag Lys													384
			ctg Leu													432
			acg Thr													480
			tcc Ser													528
			atc Ile 180													576
			aga Arg													624

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ttg Leu 225	aat Asn	gca Ala	gac Asp	ttg Leu	atg Met 230	atg Met	ttt Phe	gct Ala	cac His	aaa Lys 235	gac Asp	ccc Pro	aga Arg	gaa Glu	atc Ile 240	720
gat Asp	ccc Pro	att Ile	gtc Val	aca Thr 245	cga Arg	aga Arg	tat Tyr	tac Tyr	tat Tyr 250	tct Ser	gtc Val	aag Lys	gat Asp	att Ile 255	tca Ser	768
gtt Val	ggc Gly	ggg Gly	atg Met 260	tgc Cys	atc Ile	tgt Cys	tat Tyr	ggt Gly 265	cat His	gcc Ala	cgg Arg	gct Ala	tgt Cys 270	cca Pro	ctt Leu	816
gac Asp	cct Pro	gca Ala 275	aca Thr	aat Asn	aaa Lys	tca Ser	cgc Arg 280	tgt Cys	gag Glu	tgt Cys	gaa Glu	cat His 285	aac Asn	acc Thr	tgt Cys	864
G] À 333	gaa Glu 290	agc Ser	tgt Cys	gac Asp	agg Arg	tgc Cys 295	tgt Cys	cca Pro	gga Gly	ttc Phe	cat His 300	cag Gln	aag Lys	cct Pro	tgg Trp	912
aga Arg 305	gct Ala	gga Gly	acc Thr	ttc Phe	ctc Leu 310	acc Thr	aag Lys	tct Ser	gag Glu	tgt Cys 315	gaa Glu	gca Ala	tgc Cys	aat Asn	tgt Cys 320	960
cac His	gga Gly	aaa Lys	gct Ala	gag Glu 325	gaa Glu	tgc Cys	tat Tyr	tat Tyr	gat Asp 330	gaa Glu	act Thr	gtt Val	gct Ala	agc Ser 335	aga Arg	1008
aat Asn	cta Leu	agt Ser	tta Leu 340	aat Asn	ata Ile	cat His	gly ggg	aag Lys 345	tac Tyr	atc Ile	gga Gly	ggg Gly	ggt Gly 350	gtg Val	tgc Cys	1056
atc Ile	aac Asn	tgc Cys 355	aca Thr	cat His	aac Asn	acg Thr	gct Ala 360	gly ggg	ata Ile	aat Asn	tgt Cys	gag Glu 365	aca Thr	tgt Cys	gtt Val	1104
gat Asp	gga Gly 370	ttc Phe	ttc Phe	aga Arg	ccc Pro	aaa Lys 375	ggg Gly	gtg Val	tca Ser	cca Pro	aat Asn 380	tat Tyr	cca Pro	aga Arg	cca Pro	1152
tgc Cys 385	cag Gln	cca Pro	tgt Cys	cac His	tgt Cys 390	gat Asp	cca Pro	act Thr	ggc Gly	tcc Ser 395	ctt Leu	agt Ser	gaa Glu	gtc Val	tgt Cys 400	1200
gtc Val	aaa Lys	gat Asp	gag Glu	aaa Lys 405	tac Tyr	gcc Ala	cag Gln	cga Arg	999 Gly 410	ttg Leu	aaa Lys	cct Pro	gga Gly	tcc Ser 415	tgt Cys	1248
cac His	tgc Cys	aaa Lys	act Thr 420	ggc Gly	ttt Phe	gga Gly	ggc Gly	gtg Val 425	aac Asn	tgt Cys	gat Asp	cgc Arg	tgt Cys 430	gtc Val	agg Arg	1296
ggt Gly	tac Tyr	cat His 435	ggt	tac Tyr	cca Pro	gac Asp	tgc Cys 440	caa Gln	ccc Pro	tgt Cys	aac Asn	tgt Cys 445	agt Ser	ggc Gly	ttg Leu	1344
999	agc	aca	aat	gag	gac	cct	tgc	gtt	999	ccc	tgt	agc	tgt	aag	gag	1392

Gly	Ser 450	Thr	Asn	Gl.u	Asp	Pro 455	Cys	Val	Gly	Pro	Cys 460	Ser	Сув	Lys	Glu	
aat Asn 465	gtt Val	gaa Glu	ggt Gly	gaa Glu	gac Asp 470	tgt Cys	agt Ser	cgt Arg	tgc Cys	aaa Lys 475	tct Ser	ggt Gly	ttc Phe	ttc Phe	aac Asn 480	1440
ttg Leu	caa Gln	gaa Glu	gat Asp	aat Asn 485	cag Gln	aaa Lys	ggc Gly	tgt Cys	gag Glu 490	gag Glu	tgt Cys	ttc Phe	tgt Cys	tca Ser 495	gga Gly	1488
				tgt Cys												1536
				tgg Trp												1584
				gat Asp												1632
				cgg Arg												1680
				ctg Leu 565												1728
				tca Ser												1776
				ctg Leu												1824
				aag Lys												1872
				ctc Leu												1920
				aga Arg 645												1968
				caa Gln												2016
				gtc Val												2064

690	e	595	700		
agt ggc agc s Ser Gly Ser s 705	tct tgt gaa a Ser Cys Glu 1 710	aca tgt tgg Thr Cys Trp	cct agg cac c Pro Arg His A 715	ga aga gtt rg Arg Val	aac 2160 Asn 720
ggc acc att Gly Thr Ile	ttt ggt ggc a Phe Gly Gly 1 725	att tgt gaa Ile Cys Glu	cca tgt cag t Pro Cys Gln C 730	gc ttt gct ys Phe Ala 735	cat 2208 His
Ala Glu Ala	tgt gat gac a Cys Asp Asp 1 740	atc aca gga Ile Thr Gly 745	gaa tgt ctg a Glu Cys Leu A	ac tgt aag sn Cys Lys 750	gat 2256 Asp
			tgt ctc cct g Cys Leu Pro G 7		
gat cct act a Asp Pro Thr 7	Arg Gly Ser H	ect gaa gac Pro Glu Asp 775	tgt cag ccc t Cys Gln Pro C 780	gt gec tgt ys Ala Cys	cca 2352 Pro
			cca aca tgc c Pro Thr Cys H 795		
		Asp Glu Cys	cct att ggg t Pro Ile Gly T 810		
Arg Cys Glu			ttt gga caa c Phe Gly Gln P		
			aat gac aac c Asn Asp Asn <b>L</b> 8		
	Ser Cys Asp S		ggc tcc tgt c Gly Ser Cys L 860		
			ctc tgt gct g Leu Cys Ala A 875		
		Lys Asn Cys	caa cca tgc c Gln Pro Cys A 890		
Asn Gly Ser			aca aga act g Thr Arg Thr G		
			tgt gac gag t Cys Asp Glu C 9		
	Leu Gln Leu G		tgt ctg ccc t Cys Leu Pro C 940		

tct Ser 945	ttt Phe	61 y 999	tct Ser	aag Lys	tcc Ser 950	ttt Phe	gac Asp	tgt Cys	gaa Glu	gca Ala 955	agt Ser	G1y 999	cag Gln	tgc Cys	tgg Trp 960	2880
			gga Gly													2928
			ttc Phe 980													2976
			aac Asn			Pro					Cys					3024
Asn			gga Gly		Lys					Leu						3072
	Ser		gtc Val	Thr					Cys					Val		3120
			tct Ser					Asn					Ser			3168
		Phe	tct Ser 1060				Сув					Arg				3216
	Tyr		ctc Leu			Leu					Leu					3264
Ala			tgt Cys		Leu					Сув						3312
	Gly		tgc Cys	Ser					Val					Сув		3360
			cct Pro					Leu					Pro			3408
		Ser	tgc Cys 1140				Gly					Сув				3456
	Gly		atc Ile			Trp					Asp					3504
Leu			gtg Val		Glu					Thr						3552

gct Ala 1185	Phe	cag Gln	aaa Lys	Pro	gag Glu 190	att Ile	gtt Val	gca Ala	Lys	atg Met L195	gat Asp	gaa Glu	gtc Val	Arg	caa Gln L200	3600
gag Glu	ctc Leu	cat His	Leu	gaa Glu 1205	cct Pro	ttt Phe	tac Tyr	Trp	aaa Lys 1210	ctc Leu	cca Pro	caa Gln	Gln	ttt Phe 1215	gaa Glu	3648
999 Gly	aaa Lys	Lys	ttg Leu 220	atg Met	gct Ala	tat Tyr	Gly	ggc Gly L225	aaa Lys	ctc Leu	aag Lys	Tyr	gcc Ala L230	atc Ile	tat Tyr	3696
	Glu				gag Glu	Thr					Tyr					3744
Ile					act Thr					Arg						3792
	Ala			Leu	att Ile 1270				Thr					Glu		3840
			Glu		aaa Lys			Gly					Ile			3888
					gac Asp											3936
		1	300		_		3	1305			•	-	1310			
	Leu	atc	aag	gct	act Thr	Tyr	gga	aac		gtg	aga Arg	caa	1310 agc	cgc	att	3984
Ile tct Ser	Leu I gaa	atc Ile 315 atc	aag Lys tcc	gct Ala atg	Thr gaa Glu	Tyr 1 gta	gga Gly 1320 gct	aac Asn gaa	Val	gtg Val gga Gly	aga Arg J	caa Gln 1325 gta	agc Ser tta	cgc Arg gca	att Ile	3984 4032
Ile tct Ser I	gaa Glu 3330 cca Pro	atc Ile 315 atc Ile	aag Lys tcc Ser	gct Ala atg Met cac	Thr gaa Glu	Tyr gta Val .335	gga Gly 320 gct Ala	aac Asn gaa Glu aga	Val cca Pro tgc Cys	gtg Val gga Gly gat	aga Arg cat His 340	caa Gln 325 gta Val	agc Ser tta Leu	cgc Arg gca Ala ggc Gly	att Ile 999 Gly	
tct Ser agc Ser 1345	gaa Glu 330 cca Pro	atc Ile 315 atc Ile cca Pro	aag Lys tcc Ser gca Ala tct	gct Ala atg Met cac His	Thr gaa Glu ttg Leu	gta Val .335 ata Ile	gga Gly 320 gct Ala gaa Glu	aac Asn gaa Glu aga Arg	Val cca pro tgc Cys	gtg Val gga Gly gat Asp 355	aga Arg cat His 340 tgc Cys	caa Gln 325 gta Val cct Pro	agc Ser tta Leu cct Pro	cgc Arg gca Ala ggc Gly	att Ile 999 Gly tat Tyr 360	4032
tct Ser agc Ser 1345 tct Ser	gaa Glu 330 cca Pro ggc Gly	atc Ile 315 atc Ile cca Pro ttg Leu	aag Lys tcc Ser gca Ala tct Ser	gct Ala atg Met cac His Cys 365	gaa Glu ttg Leu 1350	gta Val .335 ata Ile acg Thr	gga Gly 320 gct Ala gaa Glu tgt Cys	aac Asn gaa Glu aga Arg gca Ala	CCA Pro tgc Cys cca Pro	gtg Val gga Gly gat Asp 355 gga Gly	aga Arg Cat His 340 tgc Cys	caa Gln 325 gta Val eet Pro tac Tyr	agc Ser tta Leu cct Pro cga Arg	cgc Arg gca Ala ggc Gly ctt Leu 1375	att Ile 999 Gly tat Tyr 1360 cgt Arg	4032
tct Ser 1345 tct Ser tct Ser	gaa Glu 3330 cca Pro ggc Gly gaa Glu	atc Ile 315 atc Ile cca Pro ttg Leu cca	aag Lys tcc Ser gca Ala tct Ser	gct Ala atg Met cac His Cys 365 ggg Gly	gaa Glu ttg Leu 350 gag Glu	Tyr 1 gta Val 335 ata Ile acg Thr act Thr	gga Gly 320 gct Ala Glu tgt Cys	aac Asn gaa Glu aga Arg gca Ala 1 gga Gly 385	Val  cca Pro  tgc Cys cca 370 cca Pro	gtg Val gga Gly gat Asp (355) gga Gly acc Thr	aga Arg cat His 340 tgc Cys ttt Phe tta Leu gat Asp	caa Gln 1325 gta Val cct Pro tac Tyr	agc Ser tta Leu cct Pro cga Arg	cgc Arg gca Ala ggc Gly ctt Leu 1375 tgt Cys	att Ile ggg Gly tat Tyr 1360 cgt Arg	4032 4080 4128
tct Ser 1 agc Ser 1345 tct Ser tct Ser	gaa Glu 330 cca Pro Gly gaa Glu tgc Cys 1 tgc Cys 410	atc Ile 315 atc Ile cca Pro ttg Leu cca Pro 3395 cag Gln	aag Lys tcc Ser gca Ala tct Ser ggt Gly 380 tgt Cys	gct Ala atg Met cac Cys 3.65 999 Gly aat Asn	Thr gaa Glu 1 ttg Leu .350 gag Glu cgg Glu cgg Gly cag Gly cag Gly	Tyr 1 gta Val 335 ata Ile acg Thr act Thr cac His 415	gga Gly 320 gct Ala gaa Glu tgt Cys cct Pro 1 agc Ser 400 cac His	aac Asn gaa Glu aga Arg gca Ala Gly 1385 agt Ser act	val cca Pro tgc Cys cca Pro cca Pro cca Pro cag Gln gct Ala	gtg Val gga Gly gat Asp 3555 gga Gly acc Thr tgt Cys	aga Arg Cat His 3340 tgc Cys ttt Phe tta Leu gat Asp 420	caa Gln 325 gta Val cct Pro tac Tyr ggg Gly 1 cct Pro 405 ttc	agc Ser tta Leu cct Pro cga Arg 1 acc Thr 390 gag Glu	cgc Arg gca Ala ggc Gly 1 ctt Leu 3.75 tgt Cys acc Thr	att Ile ggg Gly tat Tyr 360 cgt Arg gtt Val tca Ser	4032 4080 4128 4176

Cys Ala Leu Gl 1425	y Tyr Tyr Gly Ild 1430	e Val Arg Gly Leu 1435	Pro Asn Asp Cys 1440	
caa cca tgt gc Gln Pro Cys Al	t tgt cct ctg ato a Cys Pro Leu Ilo 1445	t tcg ccc agc aac e Ser Pro Ser Asn 1450	aat ttc agc ccc 4368 Asn Phe Ser Pro 1455	
tot tgt gta tt Ser Cys Val Le 146	u Glu Gly Leu Gli	a gat tac cgt tgc u Asp Tyr Arg Cys 1465	acc gcc tgc cca 4416 Thr Ala Cys Pro 1470	
agg ggc tat ga Arg Gly Tyr Gl 1475	a gga cag tac tg u Gly Gln Tyr Cys 1480	t gaa agg tgt gcc s Glu Arg Cys Ala 0	cca ggc tat act 4464 Pro Gly Tyr Thr 485	
ggc agc cca ag Gly Ser Pro Se 1490	c agc ccc gga ggo r Ser Pro Gly Gly 1495	c toc tgc caa gaa y Ser Cys Gln Glu 1500	tgt gag tgt gac 4512 Cys Glu Cys Asp	
cct tat ggc tc Pro Tyr Gly Se 1505	c cta ccg gtt ccc r Leu Pro Val Pro 1510	c tgt gac cgg gtc c Cys Asp Arg Val 1515	aca gga ctc tgc 4560 Thr Gly Leu Cys 1520	
acg tgc cgc cc Thr Cys Arg Pr	t gga gcc aca gga o Gly Ala Thr Gly 1525	a agg aag tgt gat y Arg Lys Cys Asp 1530	ggc tgc gag cac 4608 Gly Cys Glu His 1535	
	g Glu Gly Ala Gl	g tgt gtc ttt tgt u Cys Val Phe Cys 1545		
		g gct cgt cta gag u Ala Arg Leu Glu 0		
		g cct gct cca tat u Pro Ala Pro Tyr 1580		
		a ctc aag cac ctg u Leu Lys His Leu 1595		
		g ttg gca gag ggc n Leu Ala Glu Gly 1610		
	u Thr Asn Glu Lei	g cta acc aga gca u Leu Thr Arg Ala 1625		
		a gat gct gag agg n Asp Ala Glu Arg 0		
		t aaa ggg ctt gtc e Lys Gly Leu Val 1660		
		a cta aat gaa acc s Leu Asn Glu Thr		

1665	1670	1675	1680
Asp Lys Thr Ala	gag aga aac ttg Glu Arg Asn Leu 1685	g gag gag ctt caa aa n Glu Glu Leu Gln Ly 1690	ag gaa atc gac 5088 ys Glu Ile Asp 1695
cgg atg ctg aag Arg Met Leu Lys 1700	Glu Leu Arg Ser	aaa gat ctt caa a Lys Asp Leu Gln Tl 1705	ca cag aag gaa 5136 ir Gln Lys Glu 1710
gtt gct gag gat Val Ala Glu Asp 1715	gag ctc gtg gca Glu Leu Val Ala 1720	gca gaa ggc ctt co Ala Glu Gly Leu Le 172	eu Lys Arg Val
aac aag ctg ttt Asn Lys Leu Phe 1730	gga gag ccc aga Gly Glu Pro Arg 1735	gcc cag aat gaa ga Ala Gln Asn Glu As 1740	at atg gaa aag 5232 sp Met Glu Lys
gat ctc cag cag Asp Leu Gln Gln 1745	aaa ctg gca gag Lys Leu Ala Glu 1750	tac aag aac aaa ci Tyr Lys Asn Lys Lo 1755	et gat gat gct 5280 eu Asp Asp Ala 1760
Trp Asp Leu Leu		gat aaa acc cga ga Asp Lys Thr Arg As 1770	
	Asn Gln Lys Asn	atg acc ata ctg ga Met Thr Ile Leu Gi 1785	
gag gct att gaa Glu Ala Ile Glu 1795	ggt agc aaa cga Gly Ser Lys Arg 1800	caa ata gag aac ac Gln Ile Glu Asn Th 180	ır Leu Lys Glu
		aat caa ctc tta gg Asn Gln Leu Leu Gl 1820	
		att aaa act aag tt Ile Lys Thr Lys Le 1835	
Ser Glu Glu Leu		gat gac ctc gcc ca Asp Asp Leu Ala Gl 1850	
	Ala Glu Lys Val	ttc cag gct gag ag Phe Gln Ala Glu Se 1865	
cag ctg aac gac Gln Leu Asn Asp 1875	tcg tct gct gta Ser Ser Ala Val 1880	ctt gat gga atc ct Leu Asp Gly Ile Le 188	u Asp Glu Ala
		gca gcc ttc aga gc Ala Ala Phe Arg Al 1900	
att aaa gac tac Ile Lys Asp Tyr 1905	att gat gaa gct Ile Asp Glu Ala 1910	gag aaa gtg gcc ag Glu Lys Val Ala Ar 1915	a gaa gcc aaa 5760 g Glu Ala Lys 1920

Glu Leu Ala Gln G	gg gct aca aaa ct ly Ala Thr Lys Le 25	g gca aca agt cct cag ggc tta 5808 a Ala Thr Ser Pro Gln Gly Leu 1930 1935
tta aaa gaa gat g Leu Lys Glu Asp A 1940	cc aaa ggc tcc ct la Lys Gly Ser Le 194	cag aaa agc ttc agg atc ctc 5856 Gln Lys Ser Phe Arg Ile Leu 5 1950
		gtg aaa gga aat cac aat gat 5904 b Val Lys Gly Asn His Asn Asp 1965
		a act gct gac ctt aga aac agt 5952 n Thr Ala Asp Leu Arg Asn Ser 1980
		e atg gac aag tta tca gcc att 6000 Met Asp Lys Leu Ser Ala Ile 1995 2000
Thr Asn Asp Thr A		g gct gtc aaa gag aaa gcc aga 6048 n Ala Val Lys Glu Lys Ala Arg 2010 2015
		c ctg gcc cag gtt aag gac ctg 6096 L Leu Ala Gln Val Lys Asp Leu 2030
		a aac tac aat aaa ctg gca gac 6144 n Asn Tyr Asn Lys Leu Ala Asp 2045
		g aaa gat oot too aaa aac aaa 6192 L Lys Asp Pro Ser Lys Asn Lys 2060
		g aga aat cta gaa cag gaa gct 6240 l Arg Asn Leu Glu Gln Glu Ala 2075 2080
Asp Arg Leu Ile A	ac aaa ctc aag cc sp Lys Leu Lys Pro 85	c atc aag gag ctt gag gac aac 6288 o Ile Lys Glu Leu Glu Asp Asn 2090 2095
		g gaa ctg atc aac caa gct cgg 6336 s Glu Leu Ile Asn Gln Ala Arg 5 2110
		gtt tot tog gga ggt gac tgt 6384 r Val Ser Ser Gly Gly Asp Cys 2125
		g aaa gga agc tac aat aac atc 6432 s Lys Gly Ser Tyr Asn Asn Ile 2140
		c gac aac ctc ctt ttt tat ctt 6480 3 Asp Asn Leu Leu Phe Tyr Leu 2155 2160

gga agt gcc Gly Ser Ala	aaa ttt a Lys Phe 1 2165	itt gac ttt Ile Asp Phe	ctt gct Leu Ala 2170	ata gaa at Ile Glu Me	g cgc aaa gg et Arg Lys Gl 2175	c 6528 Y
Lys val Ser	ttc ctc t Phe Leu 1 2180	rp He Val	ggc tct Gly Ser 2185	gga gtt gg Gly Val Gl	jc cga gta gg y Arg Val Gl 2190	g 6576 Y
ttt cca gac Phe Pro Asp 2195	ttg acc a Leu Thr I	atc gac gac le Asp Asp 2200	Ser Tyr	tgg tac cg Trp Tyr Ar 220	gt att gaa gc g Ile Glu Al 5	a 6624 a
tca aga acg Ser Arg Thr 2210	gga aga a Gly Arg A	at gga tct Asn Gly Ser 2215	att tct Ile Ser	gtg aga go Val Arg Al 2220	t tta gat gg a Leu Asp Gl	a 6672 Y
ccc aaa gcc Pro Lys Ala 2225	Ser Met V	ta ccc agc Val Pro Ser 130	Thr Tyr	cat tca gt His Ser Va 2235	g tet eet ee 1 Ser Pro Pro 224	5
					g ttt gtt gg u Phe Val Gl 2255	
Gly Leu Thr	gga aaa a Gly Lys I 2260	le Lys Lys	gcc gat Ala Asp 2265	gct gta cg Ala Val Ar	t gtg atc acc g Val Ile Th 2270	e 6816 r
			Tyr Phe		a cct ata gg 8 Pro Ile Gl 5	
					a tgt act gto y Cys Thr Va	
	Val Glu A		Gly Thr		t gat ggt gaa e Asp Gly Gli 2320	1
ggc tat gca Gly Tyr Ala	tta gtg a Leu Val S 2325	gc cgg ccc er Arg Pro	atc cgc Ile Arg 2330	tgg tac cc Trp Tyr Pr	c aac atc tco o Asn Ile Sen 2335	7008
Thr Val Met		he Arg Thr			t ctc ctg ato a Leu Leu Met 2350	
tat ctt gcc Tyr Leu Ala 2355	aca cga g Thr Arg A	ac ctg aaa sp Leu Lys 2360	gat ttc Asp Phe	atg agt gt Met Ser Va 236	a gag ctc agt l Glu Leu Ser 5	7104
gat gga cat Asp Gly His 2370	gtg aaa g Val Lys V	tc agc tat al Ser Tyr 2375	gac ctg Asp Leu	ggc tca gg Gly Ser Gl 2380	a atg act tco y Met Thr Sei	7152
gtt gtc agc Val Val Ser 2385	aat caa a Asn Gln A 23	sn His Asn	Asp Gly	aaa tgg aa Lys Trp Ly 395	a gca ttc acg s Ala Phe Thr 2400	7
ctg tcg cgg	att cag a	aa caa gcc	aac ata	tcg att gt	c gac atc gat	7248

	Gln Lys Gln Ala 405	Asm Ile Ser I 2410	le Val Asp Ile Asp 2415	
tct aac cag gag Ser Asn Gln Glu 2420	gag aat gta gct Glu Asn Val Ala	act toa tot t Thr Ser Ser S 2425	ct gga aac aac ttt er Gly Asn Asn Phe 2430	7296
		Lys Ile Tyr P	tt ggt ggc ctg cca he Gly Gly Leu Pro 2445	7344
act ctg aga aac Thr Leu Arg Asn 2450	ttg agt atg aaa Leu Ser Met Lys 2455	gca agg cca g Ala Arg Pro G 24	aa gtc aat gtg aag lu Val Asn Val Lys 60	7392
Lys Tyr Ser Gly 2465	Cys Leu Lys Asp 2470	Ile Glu Ile S 2475	ca aga aca cct tac er Arg Thr Pro Tyr 2480	7440
Asn Ile Leu Ser			cc aaa ggc tgt tca hr Lys Gly Cys Ser 2495	7488
	Asn Thr Val Ser		ct ggt ttt gtg gag ro Gly Phe Val Glu 2510	7536
		Gly Thr Glu I	tc aat ctg tcc ttt le Asn Leu Ser Phe 2525	7584
			ga agt gga ggg aca ly Ser Gly Gly Thr 40	7632
			ca cag gct tat tat hr Gln Ala Tyr Tyr 2560	7680
Ala Ile Phe Leu		Leu Glu Val H	at ctc tcc tcg ggg is Leu Ser Ser Gly	7728
		2570	2575	
	Arg Lys Ile Val	atc aaa ccg g	2575 ag cca aat ttg ttt lu Pro Asn Leu Phe 2590	7776
Thr Arg Thr Met 2580 cat gat ggg aga	Arg Lys Ile Val	atc aaa ccg g Ile Lys Pro G 2585 cac gta gaa a His Val Glu A	ag cca aat ttg ttt lu Pro Asn Leu Phe	7776 7824
Thr Arg Thr Met 2580  cat gat ggg aga His Asp Gly Arg 2595  ttc act gtt caa	gaa cat tot gto Glu His Ser Val 2600 att gat gaa gac	atc aaa ccg g Ile Lys Pro G 2585 cac gta gaa a His Val Glu A	ag cca aat ttg ttt lu Pro Asn Leu Phe 2590  ga acc aga ggc atc rg Thr Arg Gly Ile 2605  tc caa aac ctg aca le Gln Asn Leu Thr	
Thr Arg Thr Met 2580  cat gat ggg aga His Asp Gly Arg 2595  ttc act gtt caa Phe Thr Val Gln 2610  gag gaa cag ccc	gaa cat tot gto Glu His Ser Val 2600 att gat gaa gac Ile Asp Glu Asp 2615 atc gaa gtg aaa	atc aaa ccg g Ile Lys Pro G 2585  cac gta gaa a His Val Glu A aga aga cat a Arg Arg His I 26	ag cca aat ttg ttt lu Pro Asn Leu Phe 2590  ga acc aga ggc atc rg Thr Arg Gly Ile 2605  tc caa aac ctg aca le Gln Asn Leu Thr	7824

2645		2650	2655	
tgt gtg tgg aac ctt Cys Val Trp Asn Leu 2660	Val Ile Asn S	ecc atc ccc atg Ser Ile Pro Met	gac ttt gcg cag Asp Phe Ala Gln 2670	8016
cct ata gcc ttc aaa Pro Ile Ala Phe Lys 2675	aat gcc gac a Asn Ala Asp I 2680	le Gly Arg Cys	acc tat caa aag Thr Tyr Gln Lys 2685	8064
ccc cgg gaa gat gag Pro Arg Glu Asp Glu 2690	agt gaa gca g Ser Glu Ala V 2695	tt cca gct gaa Val Pro Ala Glu 2700	gtt att gtc cag Val Ile Val Gln	8112
cct cag tcg gtg ccc Pro Gln Ser Val Pro 2705	acc cct gcc t Thr Pro Ala P 2710	tc cct ttc cca The Pro Phe Pro 2715	gtc ccc acc atg Val Pro Thr Met 2720	8160
gtg cat ggc cct tgt Val His Gly Pro Cys 2725	gtt gca gaa t Val Ala Glu S	ca gaa cca gct er Glu Pro Ala 2730	ctt ctg aca ggg Leu Leu Thr Gly 2735	8208
agc aag cag ttt ggg Ser Lys Gln Phe Gly 2740	Leu Ser Arg A			8256
gat gac acc aaa gtt Asp Asp Thr Lys Val 2755	aaa aac cgc c Lys Asn Arg L 2760	eu Thr Ile Glu	ctg gag gta cga Leu Glu Val Arg 765	8304
act gaa gct gaa tca Thr Glu Ala Glu Ser 2770	ggc ttg ctc t Gly Leu Leu P 2775	tc tac atg ggt he Tyr Met Gly 2780	cgg atc aat cat Arg Ile Asn His	8352
gct gat ttt ggt act Ala Asp Phe Gly Thr 2785				8400
tat gat ttg ggg agt Tyr Asp Leu Gly Ser 2805	Gly Ser Thr A	rg Thr Met Ile 2810	Pro Thr Lys Ile 2815	8448
aac gat ggt cag tgg Asn Asp Gly Gln Trp 2820	cac aag att a His Lys Ile L 28	ys Ile Val Arg	gtg aag cag gag Val Lys Gln Glu 2830	8496
gga att ctt tat gtg Gly Ile Leu Tyr Val 2835		er Ser Gln Thr		8544
aaa gcc gac atc ctg Lys Ala Asp Ile Leu 2850	gat gtc ggg g Asp Val Gly G 2855	gg att ctg tat ly Ile Leu Tyr 2860	gtc ggt gga ttg Val Gly Gly Leu	8592
ccg atc aac tat acc Pro Ile Asn Tyr Thr 2865	aca cgc aga a Thr Arg Arg I 870	tt ggt cca gtg le Gly Pro Val 2875	act tac agc ctg Thr Tyr Ser Leu 2880	8640
gat ggc tgt gtt agg Asp Gly Cys Val Arg 2885				8688

gac cag cct acc Asp Gln Pro Thr 2900	tcc agc ttt Ser Ser Phe	cac gtt ggg His Val Gly 2905	aca tgc ttt gc Thr Cys Phe Al 291	a Asn Ala	36
gag agt ggg act Glu Ser Gly Thr 2915	Tyr Phe Asp				84
ggg ttc atc gtt Gly Phe Ile Val 2930					132
aca aga ccc act Thr Arg Pro Thr 2945		Leu Gly Ile			081
gga atg ggt att Gly Met Gly Ile					28
aat ggc gct ggc Asn Gly Ala Gly 2980				e Pro Gly	76
cac atg tgc aat His Met Cys Asn 2995	Gly Gln Trp				24
aac cgt ctt gag Asn Arg Leu Glu 3010					72
cca aac tca gca Pro Asn Ser Ala 3025		Ala Asp Thr			.20
ggc ggt ttc cca Gly Gly Phe Pro					68
agg ttc cga ggc Arg Phe Arg Gly 3060				y Thr Ala	216
aac cgc tgg agg Asn Arg Trp Arg 3075	Leu Ile Leu			gtgt 92	62
tcaacctgta tcat	gcccga ctacc	taata aagata	gttc aatcctgagg	agaattcatc 93	322
aaaacaagta tatc	aagtta aacaa	tatac actect	atca tattaataaa	actaatgtgc 93	82
agcggccgc				93	91
<210> 12 <211> 3084 <212> PRT <213> Mus muscu	lus				

127

	)> 12 Arg		Gln	Ser 5	Gln	Ala	His	Gln	Gln 10	Arg	Gly	Leu	Phe	Pro 15	Ala
Val	Leu	Asn	Leu 20	Ala	Ser	Asn	Ala	Leu 25	Ile	Thr	Thr	Asn	Ala 30	Thr	Сув
Gly	Glu	Lys 35	Gly	Pro	Glu	Met	Tyr 40	Сув	Lys	Leu	Val	Glu 45	His	Val	Pro
Gly	Gln 50	Pro	Val	Arg	Asn	Pro 55	Gln	Сув	Arg	Ile	Сув 60	Asn	Gln	Asn	Ser
Ser 65	Asn	Pro	Tyr	Gln	Arg 70	His	Pro	Ile	Thr	Asn 75	Ala	Ile	Asp	Gly	Lys 80
Asn	Thr	Trp	Trp	Gln 85	Ser	Pro	Ser	Ile	Lys 90	Asn	Gly	Val	Glu	Tyr 95	His
Tyr	Val	Thr	Ile 100	Thr	Leu	Asp	Leu	Gln 105	Gln	Val	Phe	Gln	Ile 110	Ala	Tyr
Val	Ile	Val 115	Lys	Ala	Ala	Asn	Ser 120	Pro	Arg	Pro	Gly	Asn 125	Trp	Ile	Leu
Glu	Arg 130	Ser	Leu	Asp	Asp	Val 135	Glu	Tyr	Lys	Pro	Trp 140	Gln	Tyr	His	Ala
145			Thr		150					155					160
_			Ser	165		-	_		170			-	_	175	
		-	Ile 180					185	_				190		
		195	Arg				200					205			
	210		Ala	_	-	215	Ī		_		220	•		_	
225			Asp		230					235	•		_		240
			Val	245			-	-	250			-	_	255	
	•	-	Met 260	•		-	-	265			_		270		
		275	Thr				280			-		285			-
	290		Cys			295					300				
arg 305	Ala	GIA	Thr	Phe	10 310	Thr	ъàв	ser	Glu	315	Glu	Ala	Cys	Asn	Cys 320

His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp Glu Thr Val Ala Ser Arg

Lys Leu Leu Gln Leu Met Ile Ile Phe Glu Gly Asn Asp Leu Arg Ile

Ser Thr Ala Tyr Lys Glu Val Tyr Leu Glu Pro Ser Glu Glu His Val

Glu Glu Val Ser Leu Lys Glu Glu Ala Phe Thr Ile His Gly Thr Asn

Leu Pro Val Thr Arg Lys Asp Phe Met Ile Val Leu Thr Asn Leu Gly

615

				645					650					655	
Glu	Ile	Leu	Ile 660	Gln	Ile	Thr	Tyr	Asn 665	Leu	Gly	Met	Asp	Ala 670		Ph
Arg	Leu	Ser 675	Ser	Val	Asn	Leu	Glu 680	Ser	Pro	Val	Pro	Tyr 685		Thr	As
Arg	Arg 690	Ile	Ala	Thr	Asp	Val 695	Glu	Val	Суз	Gln	Сув 700	Pro	Pro	Gly	Ту
Ser 705	Gly	Ser	Ser	Cys	Glu 710	Thr	Суз	Trp	Pro	Arg 715	His	Arg	Arg	Val	720
Gly	Thr	Ile	Phe	Gly 725	Gly	Ile	Cys	Glu	Pro 730		Gln	Сув	Phe	Ala 735	His
Ala	Glu	Ala	Cys 740	Asp	Asp	Ile	Thr	Gly 745	Glu	Сув	Leu	Asn	Cys 750	Lys	Ası
His	Thr	Gly 755	Gly	Pro	Tyr	Сув	Asn 760	Glu	Cys	Leu	Pro	Gly 765	Phe	Tyr	Gly
Asp	Pro 770	Thr	Arg	Gly	Ser	Pro 775	Glu	Asp	Суз	Gln	Pro 780	Сув	Ala	Cys	Pro
Leu 785	Asn	Ile	Pro	Ser	Asn 790	Asn	Phe	Ser	Pro	Thr 795	Cys	His	Leu	Asp	Arg
Ser	Leu	Gly	Leu	Ile 805	Сув	Asp	Glu	Сув	Pro 810	Ile	Gly	Tyr	Thr	Gly 815	Pro
Arg	Cys	Glu	Arg 820	Cys	Ala	Glu	Gly	Tyr 825	Phe	Gly	Gln	Pro	Ser 830	Val	Pro
		835					Gln 840					845			
	850					855	Leu				860				
865					870		аұЭ			875					880
				885			Asn		890					895	
Asn	Gly	Ser	Phe 900	Ser	Glu	Asp	Сув	His 905	Thr	Arg	Thr	Gly	Gln 910	СЛа	Glu
		915					Arg 920					925			
	930					935	Arg				940				
945					950		Asp			955					960
Cys	Gln	Pro	Gly	Val 965	Ala	Gly	Lys	Lys	Cys 970	Asp	Arg	Cys	Ala	His 975	Gly

Tyr Phe Asn Phe Gln Glu Gly Gly Cys Ile Ala Cys Asp Cys Ser His 980 985 990

- Leu Gly Asn Asn Cys Asp Pro Lys Thr Gly Gln Cys Ile Cys Pro Pro 995 1000 1005
- Asn Thr Thr Gly Glu Lys Cys Ser Glu Cys Leu Pro Asn Thr Trp Gly 1010 1015 1020
- His Ser Ile Val Thr Gly Cys Lys Val Cys Asn Cys Ser Thr Val Gly 1025 1030 1035 1040
- Ser Leu Ala Ser Gln Cys Asn Val Asn Thr Gly Gln Cys Ser Cys His 1045 1050 1055
- Pro Lys Phe Ser Gly Met Lys Cys Ser Glu Cys Ser Arg Gly His Trp 1060 1065 1070
- Asn Tyr Pro Leu Cys Thr Leu Cys Asp Cys Phe Leu Pro Gly Thr Asp 1075 1080 1085
- Ala Thr Thr Cys Asp Leu Glu Thr Arg Lys Cys Ser Cys Ser Asp Gln
  1090 1095 1100
- Thr Gly Gln Cys Ser Cys Lys Val Asn Val Glu Gly Val His Cys Asp 1105 1110 1115 1120
- Arg Cys Arg Pro Gly Lys Phe Gly Leu Asp Ala Lys Asn Pro Leu Gly 1125 1130 1135
- Cys Ser Ser Cys Tyr Cys Phe Gly Val Thr Ser Gln Cys Ser Glu Ala 1140 1145 1150
- Lys Gly Leu Ile Arg Thr Trp Val Thr Leu Ser Asp Glu Gln Thr Ile 1155 1160 1165
- Leu Pro Leu Val Asp Glu Ala Leu Gln His Thr Thr Thr Lys Gly Ile
- Ala Phe Gln Lys Pro Glu Ile Val Ala Lys Met Asp Glu Val Arg Gln 1185 1190 1195 1200
- Glu Leu His Leu Glu Pro Phe Tyr Trp Lys Leu Pro Gln Gln Phe Glu 1205 1210 1215
- Gly Lys Lys Leu Met Ala Tyr Gly Gly Lys Leu Lys Tyr Ala Ile Tyr 1220 1225 1230
- Phe Glu Ala Arg Asp Glu Thr Gly Phe Ala Thr Tyr Lys Pro Gln Val 1235 1240 1245
- Ile Ile Arg Gly Gly Thr Pro Thr His Ala Arg Ile Ile Thr Arg His 1250 1255 1260
- Met Ala Ala Pro Leu Ile Gly Gln Leu Thr Arg His Glu Ile Glu Met 1265 1270 1275 1280
- Thr Glu Lys Glu Trp Lys Tyr Tyr Gly Asp Asp Pro Arg Ile Ser Arg 1285 1290 1295

Thr Val Thr Arg Glu Asp Phe Leu Asp Ile Leu Tyr Asp Ile His Tyr 1300 1305 1310

- Ile Leu Ile Lys Ala Thr Tyr Gly Asn Val Val Arg Gln Ser Arg Ile 1325 1320 1325
- Ser Glu Ile Ser Met Glu Val Ala Glu Pro Gly His Val Leu Ala Gly 1330 1335 1340
- Ser Pro Pro Ala His Leu Ile Glu Arg Cys Asp Cys Pro Pro Gly Tyr 1345 1350 1355 1360
- Ser Gly Leu Ser Cys Glu Thr Cys Ala Pro Gly Phe Tyr Arg Leu Arg 1365 1370 1375
- Ser Glu Pro Gly Gly Arg Thr Pro Gly Pro Thr Leu Gly Thr Cys Val 1380  $$1390\$
- Pro Cys Gln Cys Asn Gly His Ser Ser Gln Cys Asp Pro Glu Thr Ser 1395 1400 1405
- Val Cys Gln Asn Cys Gln His His Thr Ala Gly Asp Phe Cys Glu Arg 1410 1415 1420
- Cys Ala Leu Gly Tyr Tyr Gly Ile Val Arg Gly Leu Pro Asn Asp Cys 1425 1430 1435 1440
- Gln Pro Cys Ala Cys Pro Leu Ile Ser Pro Ser Asn Asn Phe Ser Pro 1445 1450 1455
- Ser Cys Val Leu Glu Gly Leu Glu Asp Tyr Arg Cys Thr Ala Cys Pro 1460 1465 1470
- Arg Gly Tyr Glu Gly Gln Tyr Cys Glu Arg Cys Ala Pro Gly Tyr Thr 1475 1480 1485
- Gly Ser Pro Ser Ser Pro Gly Gly Ser Cys Gln Glu Cys Glu Cys Asp 1490 1495 1500
- Pro Tyr Gly Ser Leu Pro Val Pro Cys Asp Arg Val Thr Gly Leu Cys 1505 1510 1515 1520
- Thr Cys Arg Pro Gly Ala Thr Gly Arg Lys Cys Asp Gly Cys Glu His 1525 1530 1535
- Trp His Ala Arg Glu Gly Ala Glu Cys Val Phe Cys Gly Asp Glu Cys 1540 1545 1550
- Thr Gly Leu Leu Gly Asp Leu Ala Arg Leu Glu Gln Met Thr Met 1555 \$1560\$
- Asn Ile Asn Leu Thr Gly Pro Leu Pro Ala Pro Tyr Lys Ile Leu Tyr 1570 1575 1580
- Gly Leu Glu Asn Thr Thr Gln Glu Leu Lys His Leu Leu Ser Pro Gln 1585 1590 1595 1600
- Arg Ala Pro Glu Arg Leu Ile Gln Leu Ala Glu Gly Asn Val Asn Thr \$1605\$
- Leu Val Met Glu Thr Asn Glu Leu Leu Thr Arg Ala Thr Lys Val Thr

1630

Ala Asp Gly Glu Gln Thr Gly Gln Asp Ala Glu Arg Thr Asn Ser Arg 1635 1640 1645

1625

1620

- Ala Glu Ser Leu Glu Glu Phe Ile Lys Gly Leu Val Gln Asp Ala Glu 1650 1655 1660
- Ala Ile Asn Glu Lys Ala Val Lys Leu Asn Glu Thr Leu Gly Asn Gln 1665 1670 1675 1680
- Asp Lys Thr Ala Glu Arg Asn Leu Glu Glu Leu Gln Lys Glu Ile Asp 1685 1690 1695
- Arg Met Leu Lys Glu Leu Arg Ser Lys Asp Leu Gln Thr Gln Lys Glu
- Val Ala Glu Asp Glu Leu Val Ala Ala Glu Gly Leu Leu Lys Arg Val 1715 1720 1725
- Asn Lys Leu Phe Gly Glu Pro Arg Ala Gln Asn Glu Asp Met Glu Lys 1730 1735 1740
- Asp Leu Gln Gln Lys Leu Ala Glu Tyr Lys Asn Lys Leu Asp Asp Ala 1745 1750 1755 1760
- Trp Asp Leu Leu Arg Glu Ala Thr Asp Lys Thr Arg Asp Ala Asn Arg 1765 1770 1775
- Leu Ser Ala Ala Asn Gln Lys Asn Met Thr Ile Leu Glu Thr Lys Lys 1780 1785 1790
- Glu Ala Ile Glu Gly Ser Lys Arg Gln Ile Glu Asn Thr Leu Lys Glu 1795 1800 1805
- Gly Asn Asp Ile Leu Asp Glu Ala Asn Gln Leu Leu Gly Glu Ile Asn 1810 1815 1820
- Ser Val Ile Asp Tyr Val Asp Asp Ile Lys Thr Lys Leu Pro Pro Met 1825 1830 1835 1840
- Ser Glu Glu Leu Ser Asp Lys Ile Asp Asp Leu Ala Gln Glu Ile Lys 1845 1850 1855
- Asp Arg Arg Leu Ala Glu Lys Val Phe Gln Ala Glu Ser His Ala Ala 1860 1865 1870
- Gln Leu Asn Asp Ser Ser Ala Val Leu Asp Gly Ile Leu Asp Glu Ala 1875 1880 1885
- Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala Phe Arg Ala Tyr Ser Asn 1890 1895 1900
- Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys Val Ala Arg Glu Ala Lys 1905 1910 1915 1920
- Glu Leu Ala Gln Gly Ala Thr Lys Leu Ala Thr Ser Pro Gln Gly Leu 1925 1930 1935
- Leu Lys Glu Asp Ala Lys Gly Ser Leu Gln Lys Ser Phe Arg Ile Leu 1940 1945 1950

Asn Glu Ala Lys Lys Leu Ala Asn Asp Val Lys Gly Asn His Asn Asp 1955 1960 1965

- Leu Asn Asp Leu Lys Thr Arg Leu Glu Thr Ala Asp Leu Arg Asn Ser 1970 1975 1980
- Gly Leu Leu Gly Ala Leu Asn Asp Thr Met Asp Lys Leu Ser Ala Ile 1985 1990 1995 2000
- Thr Asn Asp Thr Ala Ala Lys Leu Gln Ala Val Lys Glu Lys Ala Arg 2005 2010 2015
- Glu Ala Asn Asp Thr Ala Lys Ala Val Leu Ala Gln Val Lys Asp Leu 2020 2025 2030
- His Gln Asn Leu Asp Gly Leu Lys Gln Asn Tyr Asn Lys Leu Ala Asp 2035 2040 2045
- Ser Val Ala Lys Thr Asn Ala Val Val Lys Asp Pro Ser Lys Asn Lys 2050 2055 2060
- Ile Ile Ala Asp Ala Gly Thr Ser Val Arg Asn Leu Glu Gln Glu Ala 2065 2070 2075 2080
- Asp Arg Leu Ile Asp Lys Leu Lys Pro Ile Lys Glu Leu Glu Asp Asn 2085 2090 2095
- Leu Lys Lys Asn Ile Ser Glu Ile Lys Glu Leu Ile Asn Gln Ala Arg 2100 2105 2110
- Lys Gln Ala Asn Ser Ile Lys Val Ser Val Ser Ser Gly Gly Asp Cys 2115 2120 2125
- Val Arg Thr Tyr Arg Pro Glu Ile Lys Lys Gly Ser Tyr Asn Asn Ile 2130 2135 2140
- Val Val His Val Lys Thr Ala Val Ala Asp Asn Leu Leu Phe Tyr Leu 2145 2150 2155 2160
- Gly Ser Ala Lys Phe Ile Asp Phe Leu Ala Ile Glu Met Arg Lys Gly 2165 2170 2175
- Lys Val Ser Phe Leu Trp Ile Val Gly Ser Gly Val Gly Arg Val Gly 2180 2185 2190
- Phe Pro Asp Leu Thr Ile Asp Asp Ser Tyr Trp Tyr Arg Ile Glu Ala 2195 2200 2205
- Ser Arg Thr Gly Arg Asn Gly Ser Ile Ser Val Arg Ala Leu Asp Gly 2210 2215 2220
- Pro Lys Ala Ser Met Val Pro Ser Thr Tyr His Ser Val Ser Pro Pro 2225 2230 2235 2240
- Gly Tyr Thr Ile Leu Asp Val Asp Ala Asn Ala Met Leu Phe Val Gly
  2245 2250 2255
- Gly Leu Thr Gly Lys Ile Lys Lys Ala Asp Ala Val Arg Val Ile Thr 2260 2265 2270

Phe Thr Gly Cys Met Gly Glu Thr Tyr Phe Asp Asn Lys Pro Ile Gly 2275 2280 2285

- Leu Trp Asn Phe Arg Glu Lys Glu Gly Asp Cys Lys Gly Cys Thr Val 2290 2295 2300
- Ser Pro Gln Val Glu Asp Ser Glu Gly Thr Ile Gln Phe Asp Gly Glu 2305 2310 2315 2320
- Gly Tyr Ala Leu Val Ser Arg Pro Ile Arg Trp Tyr Pro Asn Ile Ser 2325 2330 2335
- Thr Val Met Phe Lys Phe Arg Thr Phe Ser Ser Ser Ala Leu Leu Met 2340 2345 2350
- Tyr Leu Ala Thr Arg Asp Leu Lys Asp Phe Met Ser Val Glu Leu Ser 2355 2360 2365
- Asp Gly His Val Lys Val Ser Tyr Asp Leu Gly Ser Gly Met Thr Ser 2370 2375 2380
- Val Val Ser Asn Gln Asn His Asn Asp Gly Lys Trp Lys Ala Phe Thr 2385 2390 2395 2400
- Leu Ser Arg Ile Gln Lys Gln Ala Asn Ile Ser Ile Val Asp Ile Asp 2405 \$2410\$
- Ser Asn Gln Glu Glu Asn Val Ala Thr Ser Ser Ser Gly Asn Asn Phe 2420 2425 2430
- Gly Leu Asp Leu Lys Ala Asp Asp Lys Ile Tyr Phe Gly Gly Leu Pro 2435 2440 2445
- Thr Leu Arg Asn Leu Ser Met Lys Ala Arg Pro Glu Val Asn Val Lys 2450 2455 . 2460
- Lys Tyr Ser Gly Cys Leu Lys Asp Ile Glu Ile Ser Arg Thr Pro Tyr 2465 2470 2475 2480
- Asn Ile Leu Ser Ser Pro Asp Tyr Val Gly Val Thr Lys Gly Cys Ser 2485 2490 2495
- Leu Glu Asn Val Asn Thr Val Ser Phe Pro Lys Pro Gly Phe Val Glu 2500 2505 2510
- Leu Ala Ala Val Ser Ile Asp Val Gly Thr Glu Ile Asn Leu Ser Phe \$2515\$ \$2520\$ \$2525\$
- Ser Thr Arg Asn Glu Ser Gly Ile Ile Leu Leu Gly Ser Gly Gly Thr 2530 2535 2540
- Leu Thr Pro Pro Arg Arg Lys Arg Arg Gln Thr Thr Gln Ala Tyr Tyr 2545 2550 2555 2560
- Ala Ile Phe Leu Asn Lys Gly Arg Leu Glu Val His Leu Ser Ser Gly 2565 2570 2575
- Thr Arg Thr Met Arg Lys Ile Val Ile Lys Pro Glu Pro Asn Leu Phe 2580 2585 2590
- His Asp Gly Arg Glu His Ser Val His Val Glu Arg Thr Arg Gly Ile

2595 2600 2605

Phe Thr Val Gln Ile Asp Glu Asp Arg Arg His Ile Gln Asn Leu Thr 2610 2615 2620

- Glu Glu Gln Pro Ile Glu Val Lys Lys Leu Phe Val Gly Gly Ala Pro 2625 2630 2635 2640
- Pro Glu Phe Gln Pro Ser Pro Leu Arg Asn Ile Pro Ala Phe Gln Gly
  2645 2650 2655
- Cys Val Trp Asn Leu Val Ile Asn Ser Ile Pro Met Asp Phe Ala Gln 2660 2665 2670
- Pro Ile Ala Phe Lys Asn Ala Asp Ile Gly Arg Cys Thr Tyr Gln Lys 2675 2680 2685
- Pro Arg Glu Asp Glu Ser Glu Ala Val Pro Ala Glu Val Ile Val Gln 2690 2695 2700
- Pro Gln Ser Val Pro Thr Pro Ala Phe Pro Phe Pro Val Pro Thr Met 2705 2710 2715 2720
- Val His Gly Pro Cys Val Ala Glu Ser Glu Pro Ala Leu Leu Thr Gly
  2725 2730 2735
- Ser Lys Gln Phe Gly Leu Ser Arg Asn Ser His Ile Ala Ile Val Phe 2740 2745 2750
- Asp Asp Thr Lys Val Lys Asn Arg Leu Thr Ile Glu Leu Glu Val Arg 2755 2760 2765
- Thr Glu Ala Glu Ser Gly Leu Leu Phe Tyr Met Gly Arg Ile Asn His 2770 2775 2780
- Ala Asp Phe Gly Thr Val Gln Leu Arg Asn Gly Phe Pro Phe Phe Ser 2785 2790 2795 2800
- Tyr Asp Leu Gly Ser Gly Ser Thr Arg Thr Met Ile Pro Thr Lys Ile 2805 2810 2815
- Asn Asp Gly Gln Trp His Lys Ile Lys Ile Val Arg Val Lys Gln Glu 2820 2825 2830
- Gly Ile Leu Tyr Val Asp Asp Ala Ser Ser Gln Thr Ile Ser Pro Lys 2835 2840 2845
- Lys Ala Asp Ile Leu Asp Val Gly Gly Ile Leu Tyr Val Gly Gly Leu 2850 2855 2860
- Pro Ile Asn Tyr Thr Thr Arg Arg Ile Gly Pro Val Thr Tyr Ser Leu 2865 2870 2875 2880
- Asp Gly Cys Val Arg Asn Leu His Met Glu Gln Ala Pro Val Asp Leu 2885 2890 2895
- Asp Gln Pro Thr Ser Ser Phe His Val Gly Thr Cys Phe Ala Asn Ala 2900 2905 2910
- Glu Ser Gly Thr Tyr Phe Asp Gly Thr Gly Phe Gly Lys Ala Val Gly 2915 2920 2925

Gly Phe Ile Val Gly Leu Asp Leu Leu Val Glu Phe Glu Phe Arg Thr

2935 Thr Arg Pro Thr Gly Val Leu Leu Gly Ile Ser Ser Gln Lys Met Asp 2945 2950 Gly Met Gly Ile Glu Met Ile Asp Glu Lys Leu Met Phe His Val Asp Asn Gly Ala Gly Arg Phe Thr Ala Ile Tyr Asp Ala Glu Ile Pro Gly His Met Cys Asn Gly Gln Trp Tyr Lys Val Thr Ala Lys Lys Ile Lys 3000 Asn Arg Leu Glu Leu Val Val Asp Gly Asn Gln Val Asp Ala Gln Ser 3015 3020 Pro Asn Ser Ala Ser Thr Ser Ala Asp Thr Asn Asp Pro Val Phe Val 3030 3035 Gly Gly Phe Pro Gly Gly Leu Asn Gln Phe Gly Leu Thr Thr Asn Ile 3045 3050 Arg Phe Arg Gly Cys Ile Arg Ser Leu Lys Leu Thr Lys Gly Thr Ala 3060 3065 3070 Asn Arg Trp Arg Leu Ile Leu Pro Arg Pro Trp Asn 3080 <210> 13 <211> 5613 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (118)..(5475) <221> sig peptide <222> (118) .. (180) cccggagcag ggcgagagct cgcgtcgccg gaaaggaaga cgggaagaaa gggcaggcgg 60 ctcggcgggc gtcttctcca ctcctctgcc gcgtccccgt ggctgcaggg agccggc atg ggg ctt ctc cag ttg cta gct ttc agt ttc tta gcc ctg tgc aga Met Gly Leu Leu Gln Leu Leu Ala Phe Ser Phe Leu Ala Leu Cys Arg 165 gcc cga gtg cgc gct cag gaa ccc gag ttc agc tac ggc tgc gca gaa 213 Ala Arg Val Arg Ala Gln Glu Pro Glu Phe Ser Tyr Gly Cys Ala Glu 25 ggc agc tgc tat ccc gcc acg ggc gac ctt ctc atc ggc cga gca cag Gly Ser Cys Tyr Pro Ala Thr Gly Asp Leu Leu Ile Gly Arg Ala Gln  $\,$ 40

aag Lys	ctt Leu 50	tcg Ser	gtg Val	acc Thr	tcg Ser	acg Thr 55	tgc Cys	Gly 999	ctg Leu	cac His	aag Lys 60	ccc Pro	gaa Glu	ccc Pro	tac Tyr	309
tgt Cys 65	atc Ile	gtc Val	agc Ser	cac His	ttg Leu 70	cag Gln	gag Glu	gac Asp	aaa Lys	aaa Lys 75	tgc Cys	ttc Phe	ata Ile	tgc Cys	aat Asn 80	357
tcc Ser	caa Gln	gat Asp	cct Pro	tat Tyr 85	cat His	gag Glu	acc Thr	ctg Leu	aat Asn 90	cct Pro	gac Asp	agc Ser	cat His	ctc Leu 95	att Ile	405
gaa Glu	aat Asn	gtg Val	gtc Val 100	act Thr	aca Thr	ttt Phe	gct Ala	cca Pro 105	aac Asn	cgc Arg	ctt Leu	aag Lys	att Ile 110	tgg Trp	tgg Trp	453
caa Gln	tct Ser	gaa Glu 115	aat Asn	ggt Gly	gtg Val	gaa Glu	aat Asn 120	gta Val	act Thr	atc Ile	caa Gln	ctg Leu 125	gat Asp	ttg Leu	gaa Glu	501
gca Ala	gaa Glu 130	ttc Phe	cat His	ttt Phe	act Thr	cat His 135	ctc Leu	ata Ile	atg Met	act Thr	ttc Phe 140	aag Lys	aca Thr	ttc Phe	cgt Arg	549
		gct Ala														597
ggt Gly	gtg Val	tat Tyr	aga Arg	tac Tyr 165	ttc Phe	gcc Ala	tat Tyr	gac Asp	tgt Cys 170	gag Glu	gcc Ala	tcg Ser	ttt Phe	cca Pro 175	ggc	645
		act Thr														693
		tct Ser 195														741
gct Ala	tta Leu 210	gat Asp	cct Pro	gct Ala	ttc Phe	aaa Lys 215	ata Ile	gaa Glu	gat Asp	cct Pro	tat Tyr 220	agc Ser	cca Pro	agg Arg	ata Ile	789
		tta Leu														837
		ttg Leu														885
aag Lys	tat Tyr	tat Tyr	tat Tyr 260	gca Ala	gtt Val	tat Tyr	gat Asp	atg Met 265	gtg Val	gtt Val	cga Arg	gga Gly	aat Asn 270	tgc Cys	ttc Phe	933
		ggt Gly 275														981

gaa Glu	gtg Val 290	gaa Glu	gga Gly	atg Met	gtt Val	cac His 295	gga Gly	cac His	tgc Cys	atg Met	tgc Cys 300	agg Arg	cat His	aac Asn	acc Thr	1029
aag Lya 305	ggc Gly	tta Leu	aac Asn	tgt Cys	gaa Glu 310	ctc Leu	tgc Cys	atg Met	gat Asp	ttc Phe 315	tac Tyr	cat His	gat Asp	tta Leu	cct Pro 320	1077
tgg Trp	aga Arg	cct Pro	gct Ala	gaa Glu 325	ggc Gly	cga Arg	aac Asn	agc Ser	aac Asn 330	gcc Ala	tgt Cys	aaa Lys	aaa Lys	tgt Cys 335	aac Asn	1125
tgc Cys	aat Asn	gaa Glu	cat His 340	tcc Ser	atc Ile	tct Ser	tgt Cys	cac His 345	ttt Phe	gac Asp	atg Met	gct Ala	gtt Val 350	tac Tyr	ctg Leu	1173
gcc Ala	acg Thr	ggg Gly 355	aac Asn	gtc Val	agc Ser	gga Gly	ggc Gly 360	gtg Val	tgt Cys	gat Asp	gac Asp	tgt Cys 365	cag Gln	cac His	aac Asn	1221
			ege Arg													1269
			gac Asp													1317
			ggc													1365
			ggt Gly 420													1413
			cat His													1461
			cca Pro													1509
			gga Gly													1557
			ctg Leu													1605
			tta Leu 500													1653
			gga Gly													1701
tgc	tca	tgc	cgg	cct	cac	atg	att	gga	cgt	cag	tgc	aac	gaa	gtg	gaa	1749

Cya	Ser 530	Сув	Arg	Pro	His	Met 535	Ile	Gly	Arg	Gln	Сув 540	Asn	Glu	Val	Glu	
cct Pro 545	ggt Gly	tac Tyr	tac Tyr	ttt Phe	gcc Ala 550	acc Thr	ctg Leu	gat Asp	cac His	tac Tyr 555	Leu	tat Tyr	gaa Glu	gcg Ala	gag Glu 560	1797
gaa Glu	gcc Ala	aac Asn	ttg Leu	999 565	cct Pro	ggg ggg	gtt Va <b>l</b>	agc Ser	ata Ile 570	gtg Val	gag Glu	cgg Arg	caa Gln	tat Tyr 575	atc Ile	1845
cag Gln	gac Asp	cgg Arg	att Ile 580	ccc Pro	tcc Ser	tgg Trp	act Thr	gga Gly 585	gcc Ala	ggc Gly	ttc Phe	gtc Val	cga Arg 590	gtg Val	cct Pro	1893
gaa Glu	gly ggg	gct Ala 595	tat Tyr	ttg Leu	gag Glu	ttt Phe	ttc Phe 600	att 11e	gac Asp	aac Asn	ata Ile	cca Pro 605	tat Tyr	tcc Ser	atg Met	1941
gag Glu	tac Tyr 610	gac Asp	atc Ile	cta Leu	att Ile	cgc Arg 615	tac Tyr	gag Glu	cca Pro	cag Gln	cta Leu 620	ccc Pro	gac Asp	Cac His	tgg Trp	1989
gaa Glu 625	aaa Lys	gct Ala	gtc Val	atc Ile	aca Thr 630	gtg Val	cag Gln	cga Arg	cct Pro	gga Gly 635	agg Arg	att Ile	cca Pro	acc Thr	agc Ser 640	2037
agc Ser	cga Arg	tgt Cys	ggt Gly	aat Asn 645	acc Thr	atc Ile	ccc Pro	gat Asp	gat Asp 650	gac Asp	aac Asn	cag Gln	gtg Val	gtg Val 655	tca Ser	2085
tta Leu	tca Ser	cca Pro	660 Gly ggc	tca Ser	aga Arg	tat Tyr	gtc Val	gtc Val 665	ctt Leu	cct Pro	cgg Arg	ccg Pro	gtg Val 670	tgc Cys	ttt Phe	2133
gag Glu	aag Lys	gga Gly 675	aca Thr	aac Asn	tac Tyr	acg Thr	gtg Val 680	agg Arg	ttg Leu	gag Glu	ctg Leu	cct Pro 685	cag Gln	tac Tyr	acc Thr	2181
tcc Ser	tct Ser 690	gat Asp	agc Ser	gac Asp	gtg Val	gag Glu 695	agc Ser	ccc Pro	tac Tyr	acg Thr	ctg Leu 700	atc Ile	gat Asp	tct Ser	ctt Leu	2229
gtt Val 705	ctc Leu	atg Met	cca Pro	tac Tyr	tgt Cys 710	aaa Lys	tca Ser	ctg Leu	gac Asp	atc Ile 715	ttc Phe	acc Thr	gtg Val	gga Gly	ggt Gly 720	2277
tca Ser	gga Gly	gat Asp	ggg Gly	gtg Val 725	gtc Val	acc Thr	aac Asn	agt Ser	gcc Ala 730	tgg Trp	gaa Glu	acc Thr	ttt Phe	cag Gln 735	aga Arg	2325
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Cys					Phe					Asp			cgg Arg			3189

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Tyr					Pro					Cys				ttt Phe		3669
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ctt gag gca gag gag agg gtg aat gcc tcc acc aca gaa ccc aad Leu Glu Ala Glu Glu Arg Val Asn Ala Ser Thr Thr Glu Pro Ass 1330 1335 1340	agc 4149 n Ser
act gtg gag cag tca gcc ctc atg aga gac aga gta gaa gac gt Thr Val Glu Gln Ser Ala Leu Met Arg Asp Arg Val Glu Asp Va 1345 1350 1355	
atg gag cga gaa tcc cag ttc aag gaa aaa caa gag gag cag gc Met Glu Arg Glu Ser Gln Phe Lys Glu Lys Gln Glu Glu Gln Al 1365 1370 1379	a Arg
ctc ctt gat gaa ctg gca ggc aag cta caa agc cta gac ctt to Leu Leu Asp Glu Leu Ala Gly Lys Leu Gln Ser Leu Asp Leu Se: 1380 1385 1390	
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Ser Leu Se	er Gln Val	gag gtt att Glu Val Ile 1560	Leu Gln His	Ser Ala Ala 1565	Asp Ile
gcc aga go Ala Arg Al 1570	et gag atg la Glu Met	ttg tta gaa Leu Leu Glu 1575	Glu Ala Lys	aga gca agc Arg Ala Ser 1580	aaa agt 4869 Lys Ser
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ctt tta oc	<b>.</b>	aat agg aag	ctg caa ctg	ctc ass gat	tta gaa 5349
Leu Leu Al 1730	a Gln Ala	Asn Ser Lys 1735	Leu Gln Leu 1	Leu Lys Asp 740	Leu Glu

5495

1745 1750 1760 tta gca aga ctg gaa gga gaa gtc cgt tca ctc cta aag gat ata agc Leu Ala Arg Leu Glu Gly Glu Val Arg Ser Leu Leu Lys Asp Ile Ser cag aaa gtt gct gtg tat agc aca tgc ttg taacagagga gaataaaaaa Gln Lys Val Ala Val Tyr Ser Thr Cys Leu 1780 tggctgaggt gaacaaggta aaacaactac attttaaaaa ctgacttaat gctcttcaaa 5555 ataaaacatc acctatttaa tgtttttaat cacattttgt atgagttaaa taaagccc <210> 14 <211> 1786 <212> PRT <213> Homo sapiens Met Gly Leu Leu Gln Leu Leu Ala Phe Ser Phe Leu Ala Leu Cys Arg Ala Arg Val Arg Ala Gln Glu Pro Glu Phe Ser Tyr Gly Cys Ala Glu 20 25 30 Gly Ser Cys Tyr Pro Ala Thr Gly Asp Leu Leu Ile Gly Arg Ala Gln 35 40 45Lys Leu Ser Val Thr Ser Thr Cys Gly Leu His Lys Pro Glu Pro Tyr 50 60 Cys Ile Val Ser His Leu Gln Glu Asp Lys Lys Cys Phe Ile Cys Asn 65 70 75 80 Ser Gln Asp Pro Tyr His Glu Thr Leu Asn Pro Asp Ser His Leu Ile 85 90 95 Glu Asn Val Val Thr Thr Phe Ala Pro Asn Arg Leu Lys Ile Trp Trp 100 105 110Gln Ser Glu Asn Gly Val Glu Asn Val Thr Ile Gln Leu Asp Leu Glu Ala Glu Phe His Phe Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg 135 Pro Ala Ala Met Leu Ile Glu Arg Ser Ser Asp Phe Gly Lys Thr Trp 145 155 160 Gly Val Tyr Arg Tyr Phe Ala Tyr Asp Cys Glu Ala Ser Phe Pro Gly 165 170 175 Ile Ser Thr Gly Pro Met Lys Lys Val Asp Asp Ile Ile Cys Asp Ser Arg Tyr Ser Asp Ile Glu Pro Ser Thr Glu Gly Glu Val Ile Phe Arg 200

Ala Leu Asp Pro Ala Phe Lys Ile Glu Asp Pro Tyr Ser Pro Arg Ile

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His	Thr	Leu	Gly	Asp 245	Asn	Leu	Leu	Asp	Ser 250	Arg	Met	Glu	Ile	Arg 255	Glı
Lys	Tyr	Tyr	Tyr 260	Ala	Val	Tyr	Asp	Met 265	Val	Val	Arg	Gly	Asn 270	Сув	Phe
Cys	Tyr	Gly 275	His	Ala	Ser	Glu	Cys 280	Ala	Pro	Val	Asp	Gly 285	Phe	Asn	Gl
Glu	Val 290	Glu	Gly	Met	Val	His 295	Gly	His	Сув	Met	Сув 300	Arg	His	Asn	Thi
Lув 305	Gly	Leu	Asn	Суз	Glu 310	Leu	Cys	Met	Asp	Phe 315	Tyr	His	Asp	Leu	Pro 320
Trp	Arg	Pro	Ala	Glu 325	Gly	Arg	Asn	Ser	Asn 330	Ala	Сув	Lys	Lys	Cys 335	Asr
Cys	Asn	Glu	His 340	Ser	Ile	Ser	Сув	His 345	Phe	Asp	Met	Ala	Val 350	Tyr	Lei
		355	Asn				360				-	365			
	370		Arg			375					380				
Pro 385	Glu	Arg	Asp	Ile	Arg 390	Asp	Pro	Asn	Phe	Сув 395	Glu	Arg	Cys	Thr	Суя 400
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Phe	Ser	Thr	Gly 420	Leu	Ile	Ala	Gly	Gln 425	Суз	Arg	Cys	Lys	Leu 430	Asn	Val
Glu	Gly	Glu 435	His	Cys	Asp	Val	Cys 440	Lys	Glu	Glγ	Phe	Ту <u>г</u> 445	Asp	Leu	Ser
	450		Pro			455					460				
465			Gly		470					475					480
			Leu	485					490					495	
			<b>Leu</b> 500					505					510	_	
		515	Gly				520					525			
Cys	Ser 530	Cys	Arg	Pro	His	Met 535	Ile	Gly	Arg	Gln	Cys 540	Asn	Glu	Val	Glu

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855

Gln Pro Cys Gln Cys Asn Gly His Ala Asp Asp Cys Asp Pro Val Thr 865 870 875 880

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- Arg Cys Leu Ala Gly Tyr Tyr Gly Asp Pro Ile Ile Gly Ser Gly Asp 900 905 910
- His Cys Arg Pro Cys Pro Cys Pro Asp Gly Pro Asp Ser Gly Arg Gln 915 920 925
- Phe Ala Arg Ser Cys Tyr Gln Asp Pro Val Thr Leu Gln Leu Ala Cys 930 935 940
- Val Cys Asp Pro Gly Tyr Ile Gly Ser Arg Cys Asp Asp Cys Ala Ser 945 950 955 960
- Gly Tyr Phe Gly Asn Pro Ser Glu Val Gly Gly Ser Cys Gln Pro Cys 965 970 975
- Gln Cys His Asn Asn Ile Asp Thr Thr Asp Pro Glu Ala Cys Asp Lys 980 985 990
- Glu Thr Gly Arg Cys Leu Lys Cys Leu Tyr His Thr Glu Gly Glu His 995 1000 1005
- Cys Gln Phe Cys Arg Phe Gly Tyr Tyr Gly Asp Ala Leu Arg Gln Asp 1010 1015 1020
- Cys Arg Lys Cys Val Cys Asn Tyr Leu Gly Thr Val Gln Glu His Cys 1025 1030 1035 1040
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- Arg Gly Ile Glu Thr Pro Gln Cys Asp Gln Ser Thr Gly Gln Cys Val
- Cys Val Glu Gly Val Glu Gly Pro Arg Cys Asp Lys Cys Thr Arg Gly 1155 . 1160 1165
- Tyr Ser Gly Val Phe Pro Asp Cys Thr Pro Cys His Gln Cys Phe Ala 1170 1175 1180
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- Thr Glu Cys Gly Gly Pro Asn Cys Arg Thr Asp Glu Gly Glu Arg Lys 1410 1415 1420
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- Glu Val Glu Gln Leu Ser Lys Met Val Ser Glu Ala Lys Leu Arg Ala 1460 1465 1470
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- Thr Lys Glu Lys Met Asp Lys Ser Asn Glu Glu Leu Arg Asn Leu Ile 1490 1495 1500
- Lys Gln Ile Arg Asn Phe Leu Thr Gln Asp Ser Ala Asp Leu Asp Ser 1505 1510 1515 1520

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- Ser Leu Ser Gln Val Glu Val Ile Leu Gln His Ser Ala Ala Asp Ile 1555 1560 1565
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- Glu Ala Glu Lys Ala Gln Val Ala Ala Glu Lys Ala Ile Lys Gln Ala 1605 1610 1615
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- Glu Thr Ala Ala Ser Glu Glu Thr Leu Phe Asn Ala Ser Gln Arg Ile 1635 1640 1645
- Ser Glu Leu Glu Arg Asn Val Glu Glu Leu Lys Arg Lys Ala Ala Gln 1650 1655 1660
- Asn Ser Gly Glu Ala Glu Tyr Ile Glu Lys Val Val Tyr Thr Val Lys 1665 1670 1675 1680
- Gln Ser Ala Glu Asp Val Lys Lys Thr Leu Asp Gly Glu Leu Asp Glu 1685 1690 1695
- Lys Tyr Lys Lys Val Glu Asn Leu Ile Ala Lys Lys Thr Glu Glu Ser 1700 1705 1710
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- Leu Leu Ala Gln Ala Asn Ser Lys Leu Gln Leu Leu Lys Asp Leu Glu 1730 1735 1740
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							aag Lys 120									384
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							ttt Phe									672
							gaa Glu									720

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					gac Asp 470											1440

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		cag Gln														1872
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		agc Ser 675														2064
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.=

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gat tot ota cag Asp Ser Leu Gln 1265	aca gaa gcc Thr Glu Ala 1270	Glu Ser Leu	gac aac act gt Asp Asn Thr Va 1275	g aaa gaa 1 Lys Glu 1280	3840
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Ser Glu Cys Ala Pro Val Asp Gly Phe Asn Glu Glu Val Glu Gly Met 260 265 270

Val His Gly His Cys Met Cys Arg His Asn Thr Lys Gly Leu Asn Cys 275 280 285

Glu Leu Cys Met Asp Phe Tyr His Asp Leu Pro Trp Arg Pro Ala Glu 290 295 300

Gly Arg Asn Ser Asn Ala Cys Lys Lys Cys Asn Cys Asn Glu His Ser 305 310 315 320

Ile Ser Cys His Phe Asp Met Ala Val Tyr Leu Ala Thr Gly Asn Val 325 330 335

Ser Gly Gly Val Cys Asp Asp Cys Gln His Asn Thr Met Gly Arg Asn 340 345 350

Cys Glu Gln Cys Lys Pro Phe Tyr Tyr Gln His Pro Glu Arg Asp Ile 355 360 365

Arg Asp Pro Asn Phe Cys Glu Arg Cys Thr Cys Asp Pro Ala Gly Ser 370 380

Gln Asn Glu Gly Ile Cys Asp Ser Tyr Thr Asp Phe Ser Thr Gly Leu 385 390 395 400

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Gly Cys Lys Ser Cys Ala Cys Asn Pro Leu Gly Thr Ile Pro Gly Gly
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Asn Pro Cys Asp Ser Glu Thr Gly His Cys Tyr Cys Lys Arg Leu Val 450 450

Thr Gly Gln His Cys Asp Gln Cys Leu Pro Glu His Trp Gly Leu Ser

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1140 1145 1150

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cgg Arg																2769
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Lys Leu Ser Val Thr Ser Thr Cys Gly Leu His Lys Pro Glu Pro Tyr Cys Ile Val Ser His Leu Gln Glu Asp Lys Lys Cys Phe Ile Cys Asp 65 70 75 80 Ser Arg Asp Pro Tyr His Glu Thr Leu Asn Pro Asp Ser His Leu Ile Glu Asn Val Val Thr Thr Phe Ala Pro Asn Arg Leu Lys Ile Trp Trp Gln Ser Glu Asn Gly Val Glu Asn Val Thr Ile Gln Leu Asp Leu Glu 115 120 125 Ala Glu Phe His Phe Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg Pro Ala Ala Met Leu Ile Glu Arg Ser Ser Asp Phe Gly Lys Thr Trp 145 150 155 160 Gly Val Tyr Arg Tyr Phe Ala Tyr Asp Cys Glu Ser Ser Phe Pro Gly 165 170 175Ile Ser Thr Gly Pro Met Lys Lys Val Asp Asp Ile Ile Cys Asp Ser 180 185 190 Arg Tyr Ser Asp Ile Glu Pro Ser Thr Glu Gly Glu Val Ile Phe Arg Ala Leu Asp Pro Ala Phe Lys Ile Glu Asp Pro Tyr Ser Pro Arg Ile 210 215 220 Gln Asn Leu Leu Lys Ile Thr Asn Leu Arg Ile Lys Phe Val Lys Leu 225 230 235 240 His Thr Leu Gly Asp Asn Leu Leu Asp Ser Arg Met Glu Ile Arg Glu 245 250 255 Lys Tyr Tyr Tyr Ala Val Tyr Asp Met Val Val Arg Gly Asn Cys Phe 260 265 270Cys Tyr Gly His Ala Ser Glu Cys Ala Pro Val Asp Gly Val Asn Glu 275 280 285 Glu Val Glu Gly Met Val His Gly His Cys Met Cys Arg His Asn Thr Lys Gly Leu Asn Cys Glu Leu Cys Met Asp Phe Tyr His Asp Leu Pro Trp Arg Pro Ala Glu Gly Arg Asn Ser Asn Ala Cys Lys Lys Cys Asn 325  $\phantom{\bigg|}330\phantom{\bigg|}$  335 Cys Asn Glu His Ser Ser Ser Cys His Phe Asp Met Ala Val Phe Leu 340 345 350Ala Thr Gly Asn Val Ser Gly Gly Val Cys Asp Asn Cys Gln His Asn

Thr Met Gly Arg Asn Cys Glu Gln Cys Lys Pro Phe Tyr Phe Gln His

370 375 380

Pro Glu Arg Asp Ile Arg Asp Pro Asn Leu Cys Glu Pro Cys Thr Cys 385 390 395 400

Asp Pro Ala Gly Ser Glu Asn Gly Gly Ile Cys Asp Gly Tyr Thr Asp 405 410 415

Phe Ser Val Gly Leu Ile Ala Gly Gln Cys Arg Cys Lys Leu His Val

Glu Gly Glu Arg Cys Asp Val Cys Lys Glu Gly Phe Tyr Asp Leu Ser 435 440 445

Ala Glu Asp Pro Tyr Gly Cys Lys Ser Cys Ala Cys Asn Pro Leu Gly
450 455 460

Thr Ile Pro Gly Gly Asn Pro Cys Asp Ser Glu Thr Gly Tyr Cys Tyr 465 470 475 480

Cys Lys Arg Leu Val Thr Gly Gln Arg Cys Asp Gln Cys Leu Pro Gln 485 490 495

His Trp Gly Leu Ser Asn Asp Leu Asp Gly Cys Arg Pro Cys Asp Cys 500 505 510

Asp Leu Gly Gly Ala Leu Asn Asn Ser Cys Ser Glu Asp Ser Gly Gln 515 520 525

Cys Ser Cys Leu Pro His Met Ile Gly Arg Gln Cys Asn Glu Val Glu 530 535 540

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gag Glu	gtg Val	gag Glu	tcc Ser	Gly	tac Tyr	tac Tyr	ttc Phe	acc Thr	Thr	ctg Leu	gac Asp	cac His	tac Tyr	atc Ile	tac Tyr	1488
				485					490					495	-	
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Glu	Ala	gag Glu att Ile 515	Glu 500 cag	gcc Ala gac	Asn	Leu	Gly	Pro 505 tcc	gga Gly tgq	Val aca	Val gga	gtg Val cct	gtg Val 510	gaa Glu ttc	agg Arg	1536 1584
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cag Gln cgg Arg tat Tyr 545	tac Tyr gtg Val 530 tcc Ser	att Ile 515 cct Pro	Glu 500 cag Gln gaa Glu gag Glu	gcc Ala gac Asp ggg Gly tat Tyr	cgc Arg gct Ala gaa Glu 550	att Ile tat Tyr 535 atc Ile	CCt Pro 520 ttg Leu ctg Leu	Pro 505 tcc Ser gag Glu att Ile	gga Gly tgg Trp ttt Phe cgc Arg	aca Thr ttc Phe tat Tyr 555	gga Gly att Ile 540 gag Glu	gtg Val cct Pro 525 gac Asp cca Pro	gtg Val 510 ggc Gly aac Asn cag	gaa Glu ttc Phe ata Ile ctg Leu aag	agg Arg gtc Val cca Pro ccg Pro 560 att	1584 1632
cag Gln cgg Arg tat Tyr 545 gac Asp	tac Tyr gtg Val 530 tcc Ser cac His	att Ile 515 cct Pro atg Met	Glu 500 cag Gln gaa Glu gag Glu	gcc Ala gac Asp ggg Gly tat Tyr aaa Lys 565	Asn cgc Arg gct Ala gaa Glu 550 gct Ala	att Ile tat Tyr 535 atc Ile gtc Val	cct Pro 520 ttg Leu ctg Leu	Pro 505 tcc Ser gag Glu att lle act Thr	gga Gly tgg Trp ttt Phe cgc Arg gta Val 570 gtt	Val aca Thr ttc Phe tat Tyr 555 cag Gln	yal gga Gly att Ile 540 gag Glu cgg Arg	gtg Val cct Pro 525 gac Asp cca Pro	gtg Val 510 ggc Gly aac Asn cag Gln ggg	gaa Glu ttc Phe ata Ile ctg Leu aag Lys 575	agg Arg gtc Val cca Pro ccg Pro 560 att Ile cag	1584 1632 1680

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aac tgc gaa agg tgc ctg gct ggc tac tac ggt gat ccc atc att ggg Asn Cys Glu Arg Cys Leu Ala Gly Tyr Tyr Gly Asp Pro Ile Ile Gly

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gga Gly 865	cga Arg	cag Gln	ttt Phe	gcc Ala	agg Arg 870	agc Ser	tgt Cys	tat Tyr	caa Gln	gac Asp 875	ccc Pro	gtc Val	act Thr	ctc Leu	cag Gln 880	2640
ctt Leu	gcg Ala	tgt Cys	gtt Val	tgt Cys 885	gat Asp	cct Pro	gly ggg	tac Tyr	att Ile 890	ggc Gly	tcc Ser	aga Arg	tgt Cys	gat Asp 895	gac Asp	2688
tgt Cys	gcc Ala	tct Ser	gga Gly 900	ttt Phe	ttt Phe	ggc Gly	aat Asn	ccç Pro 905	tca Ser	gac Asp	ttt Phe	gly aaa	ggt Gly 910	tca Ser	tgt Cys	2736
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			cya Cya													2928
			aat Asn 980													2976
			ctt Leu			Val					Cys					3024
Pro			tgg Trp		Leu					Gly						3072
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			tgc Cys					Gly					Ser			3168
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	двр		agg Arg			Glu					Asp					3264

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acc Thr 1105	Arg	ggt Gly	tac Tyr	Ser	ggg Gly L <b>1</b> 10	gtc Val	ttt Phe	cct Pro	Asp	tgc Cys 1115	aca Thr	ccc Pro	tgc Cys	His	cag Gln 1120	3360
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ggt Gly	${\tt Pro}$	tac Tyr 1155	cga Arg	gag Glu	acc Thr	Val	gac Asp 1160	tct Ser	gta Val	gag Glu	Lys	aaa Lys 1165	gtc Val	aat Asn	gag Glu	3504
Ile		gac Asp			Ala					Ala						3552
	Gly	att Ile		Phe					Lys					Val		3600
		atg Met	Ala					Lys					Ala			3648
		agc Ser					Leu					Ala				3696
	Leu	gac Asp 1235				Lys					Gln					3744
Lys		tcc Ser			Gln					Ser						3792
	Met	tct Ser		Glu					Val					Thr		3840
		agc Ser	Thr					Ala					Arg			3886
		Met					Ser					Gln			gaa Glu	3936
	Ala	cgc Arg 1315				Glu					Leu					3984
ctg	tcg	gct	gct	gca	cag	atg	acc	tgt	gga	aca	cct	cca	999	gct	gac	4032

	Lau Car	3) a 3) a	N10 G1-	Mark Miles		<b>~</b> \ -		
	1330	AIG AIG		1335	Cys Gly	1340	Prc Gly Ala	Asp
	tgt tct Cys Ser 1345	gaa agt Glu Ser	gaa tgt Glu Cys 1350	Gly Gly	Pro Asn	tgc aga Cys Arg 1355	act gac gaa Thr Asp Glu	gga 4080 Gly 1360
	gag aag Glu Lys	Lys Cys	999 999 Gly Gly 1365	cct ggc Pro Gly	tgt ggt Cys Gly 1370	ggt ctg Gly Leu	gtc act gtg Val Thr Val 1375	gcc 4128 Ala
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	Ala Leu	gct gaa Ala Glu 1395	gtc gaa Val Glu	cag ctc Gln Leu 1400	Ser Lys	Met Val	tct gaa gca Ser Glu Ala 405	aaa 4224 Lys
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				Lys Val	Asp Lys		gag gac ctg Glu Asp Leu 1	
		Ile Lys					gat agt gct Asp Ser Ala 1455	
				Val Ala			aaa agt gga Lys Ser Gly 1470	
	Ala Ser				Asn Leu	Thr Glu	gac att cgg Asp Ile Arg 485	
			Leu Ser				cag cag agt Gln Gln Ser	
					Leu Leu		gct aag aga Ala Lys Arg ]	
		Ser Ala					atg gtg aag Met Val Lys 1535	
1				Lys Ala			gag aag gcg Glu Lys Ala 1550	
	Lys Gln				Gly Thr	Gln Asn	ctg cta aca Leu Leu Thr 565	
							acc aac gcc Thr Asn Ala	

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1570	1575	1580	
cag cgc atc age Gln Arg Ile Ser 1585	c aag ctt gag agg aac r Lys Leu Glu Arg Asn 1590	gtg gaa gag ctt aag cgt aaa Val Glu Glu Leu Lys Arg Lys 1595 1600	4800
get gee cag aad Ala Ala Gin Asi	n Ser Gly Glu Ala Glu	tat atc gaa aaa gta gta tat Tyr Ile Glu Lys Val Val Tyr 1610 1615	4848
tct gta aaa cag Ser Val Lys Gli 1620	n Asn Ala Asp Asp Val	aaa aag act cta gat ggc gaa Lys Lys Thr Leu Asp Gly Glu 1630	4896
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		agc aag ctc cag ctg ttg gaa Ser Lys Leu Gln Leu Leu Glu 1675 1680	5040
	Lys Tyr Glu Asp Asn	caa aaa tac tta gaa gat aaa Gln Lys Tyr Leu Glu Asp Lys 1690 1695	5088
	ı Val Arg Leu Glu Gly	gag gtt cgc tcc ctc ctt aag Glu Val Arg Ser Leu Leu Lys 1710	5136
	g aaa gtt gcg gtt tac 1 Lys Val Ala Val Tyr 1720	agc acc tgc tta taacaggaag Ser Thr Cys Leu 1725	5185
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Ile Trp Trp Glr	Ser Glu Asn Gly Val	Glu Asn Val Thr Ile Gln Leu	

Asp Leu Glu Ala Glu Phe His Phe Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg Pro Ala Ala Met Leu Ile Glu Arg Ser Ser Asp Phe Gly
85 • 90 95 Lys Thr Trp Gly Val Tyr Arg Tyr Phe Ala Tyr Asp Cys Glu Ser Ser 105 Phe Pro Gly Ile Ser Thr Gly Pro Met Lys Lys Val Asp Asp Ile Ile 115 120 125 Cys Asp Ser Arg Tyr Ser Asp Ile Glu Pro Ser Thr Glu Gly Glu Val Pro Arg Ile Gln Asn Leu Leu Lys Ile Thr Asn Leu Arg Ile Lys Phe 165 170 175 Val Lys Leu His Thr Leu Gly Asp Asn Leu Leu Asp Ser Arg Met Glu 180 185 190 Ile Arg Glu Lys Tyr Tyr Tyr Ala Val Tyr Asp Met Val Val Arg Gly 195 200 205 Asn Cys Phe Cys Tyr Gly His Ala Ser Glu Cys Ala Pro Val Asp Gly 210 215 220 Val Asn Glu Glu Val Glu Gly Met Val His Gly His Cys Met Cys Arg His Asn Thr Lys Gly Leu Asn Cys Glu Leu Cys Met Asp Phe Tyr His 245 250 255 Asp Leu Pro Trp Arg Pro Ala Glu Gly Arg Asn Ser Asn Ala Cys Lys 265 Lys Cys Asn Cys Asn Glu His Ser Ser Ser Cys His Phe Asp Met Ala 280 Val Phe Leu Ala Thr Gly Asn Val Ser Gly Gly Val Cys Asp Asn Cys Gln His Asn Thr Met Gly Arg Asn Cys Glu Gln Cys Lys Pro Phe Tyr Phe Gln His Pro Glu Arg Asp Ile Arg Asp Pro Asn Leu Cys Glu Pro 325 330 335 Cys Thr Cys Asp Pro Ala Gly Ser Glu Asn Gly Gly Ile Cys Asp Gly 340 345 350 Tyr Thr Asp Phe Ser Val Gly Leu Ile Ala Gly Gln Cys Arg Cys Lys 355 360 365Leu His Val Glu Gly Glu Arg Cys Asp Val Cys Lys Glu Gly Phe Tyr 370 375 380

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Ile His Gln Thr Gly Leu Ala Cys Glu Cys Asp Pro Gln Gly Ser Leu 705 710 715 720 Ser Ser Val Cys Asp Pro Asn Gly Gly Gln Cys Gln Cys Arg Pro Asn 725 730 735 Val Val Gly Arg Thr Cys Asn Arg Cys Ala Pro Gly Thr Phe Gly Phe 740 745 750 Gly Pro Asn Gly Cys Lys Pro Cys Asp Cys His Leu Gln Gly Ser Ala Ser Ala Phe Cys Asp Ala Ile Thr Gly Gln Cys His Cys Phe Gln Gly 11e Tyr Ala Arg Gln Cys Asp Arg Cys Leu Pro Gly Tyr Trp Gly Phe 785 790 795 800 Pro Ser Cys Gln Pro Cys Gln Cys Asn Gly His Ala Leu Asp Cys Asp 805 810 815 Thr Val Thr Gly Glu Cys Leu Ser Cys Gln Asp Tyr Thr Thr Gly His 820 825 830 Asn Cys Glu Arg Cys Leu Ala Gly Tyr Tyr Gly Asp Pro Ile Ile Gly 835 840 845 Ser Gly Asp His Cys Arg Pro Cys Pro Cys Pro Asp Gly Pro Asp Ser 850 855 860 Gly Arg Gln Phe Ala Arg Ser Cys Tyr Gln Asp Pro Val Thr Leu Gln 865 870 880 Leu Ala Cys Val Cys Asp Pro Gly Tyr Ile Gly Ser Arg Cys Asp Asp 890 895 Cys Ala Ser Gly Phe Phe Gly Asn Pro Ser Asp Phe Gly Gly Ser Cys 900 910 Gln Pro Cys Gln Cys His His Asn Ile Asp Thr Thr Asp Pro Glu Ala 915 920 925 Cys Asp Lys Asp Thr Gly Arg Cys Leu Lys Cys Leu Tyr His Thr Glu Gly Asp His Cys Gln Leu Cys Gln Tyr Gly Tyr Tyr Gly Asp Ala Leu 945 950 955 960 Arg Gln Asp Cys Arg Lys Cys Val Cys Asn Tyr Leu Gly Thr Val Lys 965 970 975 Glu His Cys Asn Gly Ser Asp Cys His Cys Asp Lys Ala Thr Gly Gln Cys Ser Cys Leu Pro Asn Val Ile Gly Gln Asn Cys Asp Arg Cys Ala 1000 Pro Asn Thr Trp Gln Leu Ala Ser Gly Thr Gly Cys Gly Pro Cys Asn 1015

Cys Asn Ala Ala His Ser Phe Gly Pro Ser Cys Asn Glu Phe Thr Gly

1025 1030 1035 1040

- Gln Cys Gln Cys Met Pro Gly Phe Gly Gly Arg Thr Cys Ser Glu Cys 1045 1050 1055
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- Cys Asp Pro Arg Gly Ile Glu Thr Pro Gln Cys Asp Gln Ser Thr Gly
- Gln Cys Val Cys Val Glu Gly Val Glu Gly Pro Arg Cys Asp Lys Cys 1090 1095 1100
- Thr Arg Gly Tyr Ser Gly Val Phe Pro Asp Cys Thr Pro Cys His Gln 1105 1110 1115 1120
- Cys Phe Ala Leu Trp Asp Ala Ile Ile Gly Glu Leu Thr Asn Arg Thr 1125 1130 1135
- His Lys Phe Leu Glu Lys Ala Lys Ala Leu Lys Ile Ser Gly Val Ile 1140 1145 1150
- Gly Pro Tyr Arg Glu Thr Val Asp Ser Val Glu Lys Lys Val Asn Glu 1155 1160 1165
- Ile Lys Asp Ile Leu Ala Gln Ser Pro Ala Ala Glu Pro Leu Lys Asn 1170 1175 1180
- Ile Gly Ile Leu Phe Glu Glu Ala Glu Lys Leu Thr Lys Asp Val Thr 1185 1190 1195 1200
- Glu Lys Met Ala Gln Val Glu Val Lys Leu Thr Asp Thr Ala Ser Gln 1205 1210 1215
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- Pro Asn Ser Thr Val Glu Gln Ser Ala Leu Thr Arg Asp Arg Val Glu 1285 1290 1295
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- Cys Ser Glu Ser Glu Cys Gly Gly Pro Asn Cys Arg Thr Asp Glu Gly 1345 1350 1355 1360

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- Ala Leu Ala Glu Val Glu Gln Leu Ser Lys Met Val Ser Glu Ala Lys 1395 1400 1405
- Val Arg Ala Asp Glu Ala Lys Gln Asn Ala Gln Asp Val Leu Leu Lys 1410 1415 1420
- Thr Asn Ala Thr Lys Glu Lys Val Asp Lys Ser Asn Glu Asp Leu Arg 1425 1430 1435 1440
- Asn Leu Ile Lys Gln Ile Arg Asn Phe Leu Thr Glu Asp Ser Ala Asp 1445 1450 1455
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- Arg Val Glu Thr Leu Ser Gln Val Glu Val Ile Leu Gln Gln Ser Ala 1490 1495 1500
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- Ser Val Lys Gln Asn Ala Asp Asp Val Lys Lys Thr Leu Asp Gly Glu 1620 1625 1630
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- Glu Giu Ser Ala Asp Ala Arg Arg Lys Ala Glu Leu Leu Gln Asn Glu 1650 1655 1660
- Ala Lys Thr Leu Leu Ala Gln Ala Asn Ser Lys Leu Gln Leu Leu Glu 1665 1670 1675 1680

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gac tac aac cag gcc gac acc acc tgg tgg caa agc cag acc atg

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				gac Asp												724
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				cag Gln												820
				ggc Gly												868
				gaa Glu												916
				acc Thr												964
				ctg Leu 240												1012
				ctg Leu												1060
				tcc Ser												1108
ggc Gly	aga Arg 285	tgt Cys	aaa Lys	tgt Cys	aat Asn	gga Gly 290	cac His	gca Ala	agc Ser	gag Glu	tgt Cys 295	atg Met	aag Lys	aac Asn	gaa Glu	1156
				gtg Val												1204
				ctt Leu 320												1252
				gcc Ala												1300
				tac Tyr												1348

	w	O 00/	06731	,												PCT/I	JS00/11
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						ccc Pro											1636
•						tgc Cys 465											1684
						ttt Phe											1732
						tgc Сув											1780
						tat Tyr											1828
						gaa Glu											1876
7						caa Gln 545											1924
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						ctc Leu											2020

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				gtc Val												2164
				acc Thr 640												2212
				ata Ile												2260
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				gag Glu												2356
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agt Ser 780	Сув	gct Ala	gtt Val	gtt Val	ccc Pro 785	aag Lys	aca Thr	aag Lys	gag Glu	gtg Val 790	Val	tgc Cys	acc Thr	aac Asn	tgt Cys 795	2644
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	Tyr			Ser					Gln		tgt Cys			Cys		3364
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	Gln					Arg					gag Glu					3508
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			gag act gga aac tt Glu Thr Gly Asn Le 113	u Ala
Glu Gln Ala A			gag cgg ttg att ga Glu Arg Leu Ile Gl 1145	
gca tcc aga g Ala Ser Arg G 1150	gaa ctt gag aas Blu Leu Glu Lys	a gca aaa gtc 3 Ala Lys Val 1155	gct gct gcc aat gt Ala Ala Ala Asn Va 1160	g tca 3748 il Ser
		r Gly Asp Pro	aac aac atg act ct Asn Asn Met Thr Le 1175	
		ı Ala Glu Arg	cat aaa cag gaa go His Lys Gln Glu Al 1190	
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Tyr Asn Leu I  12  gag att gaa g	Leu Leu Arg Th 215 gag ott aat ag	r Leu Ala Gly 1220 g aag tat gaa	Glu Asn Gln Thr Al	tc tca 3988
gag att gaa g Glu Ile Glu C 1230 cag gat ctg g	Seu Leu Arg Th 215 gag ctt aat ag Glu Leu Asn Ar gaa aaa caa gc	r Leu'Ala Gly 1220 g aag tat gaa g Lys Tyr Glu 1235 t gcc cga gta a Ala Arg Val	Glu Asn Gln Thr Al 1225 caa gcg aag aac at Gln Ala Lys Asn Il	te tca 3988 te Ser
Tyr Asn Leu I  gag att gaa g Glu Ile Glu 1230  cag gat ctg g Gln Asp Leu G 1245  gcc ggt gac a	Jeu Leu Arg Th Jag ctt aat ag Ju Leu Asn Arg Ju Leu Asn Arg Ju Lys Gln Al 125 Ju Lys Gln Al	g aag tat gaa g Lys Tyr Glu 1235 t gcc cga gta a Ala Arg Val	Calu Asn Gln Thr Al 1225 caa gcg aag aac at Gln Ala Lys Asn Il 1240 cat gag gag gcc aa His Glu Glu Ala Ly	cc tca 3988 te Ser  aa agg 4036 vs Arg
gag att gaa g Glu Ile Glu G 1230  cag gat ctg g Gln Asp Leu G 1245  gcc ggt gac a Ala Gly Asp I 1260  cct ttg gac t	gag ctt aat agg Glu Leu Asn Arg gaa aaa caa gc Glu Lys Gln Al. 125 aaa gct gtg ga Lys Ala Val Gl 1265 tct gag aca ct	g aag tat gaag Lys Tyr Glu 1235  t gcc cga gta a Ala Arg Val 0 g atc tat gcc u Ile Tyr Ala	caa gcg aag aac at ac gag gtg gct cag ctg gcg gct cag ct Ser Val Ala Gln Le Ly ac aat aac at	ta Phe  c tca 3988 te Ser  aa agg 4036 vs Arg  g agc 4084 eu Ser 1275 ag atg 4132 vs Met
gag att gaa g Glu Ile Glu G 1230  cag gat ctg g Gln Asp Leu G 1245  gcc ggt gac a Ala Gly Asp I 1260  cct ttg gac t Pro Leu Asp S gaa gct gag a Glu Ala Glu A	gag ctt aat agg Glu Leu Asn Arg gaa aaa caa gc Glu Lys Gln Al. 125 aaa gct gtg ga Lys Ala Val Gl 1265 cct gag aca ct Ser Glu Thr Le 1280 aat ctg gaa ca	g aag tat gaag Lys Tyr Glu 1235  t gcc cga gta a Ala Arg Val 0 g atc tat gcc u Ile Tyr Ala g gag aat gaa u Glu Asn Glu 1285 a ctg att gac	caa gcg aag aac at ac gag gtg gct cag ctg gcg gct cag ct Ser Val Ala Gln Le Ly ac aat aac at	ac tca 3988 te Ser  aa agg 4036 /s Arg  ag agc 4084 eu Ser 1275 ag atg 4132 /s Met 90
gag att gaa g Glu Ile Glu G 1230  cag gat ctg g Gln Asp Leu G 1245  gcc ggt gac a Ala Gly Asp I 1260  cct ttg gac t Pro Leu Asp S  gaa gct gag a Glu Ala Glu A gag gac ctc a	gag ctt aat agglu Leu Asn Ard gaa aaa caa gc Glu Lys Gln Al. 125 aaa gct gtg ga Lys Ala Val Gl 1265 tct gag aca ct Ser Glu Thr Le 1280 aat ctg gaa ca Asn Leu Glu Gl 295	g aag tat gaag Lys Tyr Glu 1235  t gcc cga gta a Ala Arg Val 0  g atc tat gcc u Ile Tyr Ala g gag aat gaa u Glu Asn Glu 1285 a ctg att gac n Leu Ile Asp 1300 g aga ggg aae	caa gcg aag aac at Gln Ala Lys Asn Il 1240  cat gag gag gcc aa His Glu Glu Ala Ly 1255  agc gtg gct cag ct Ser Val Ala Gln Le 1270  gca aat aac ata aa 1240  Ala Asn Asn Ile Ly 1256  cag aaa tta aaa ga 1260 Gln Lys Leu Lys As	ac tca 3988 te Ser  aa agg 4036 ss Arg  ag agc 4084 teu Ser 1275 ag atg 4132 ss Met 200 at tat 4180 ap Tyr ag aac 4228

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		cag acc atc act gaa Gln Thr Ile Thr Glu 1400	
		ctg ggc agt gct gcg Leu Gly Ser Ala Ala 1415	
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Val Gln Lys Asn	gcc acc agc acc Ala Thr Ser Thr 440	aag gca gaa gct gaa Lys Ala Glu Ala Glu 1445	aga act ttt 4612 Arg Thr Phe 1450
	Asp Leu Asp Asn	gag gtg aac aat atg Glu Val Asn Asn Met .460	
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		gct tca cag gct gct Ala Ser Gln Ala Ala 1495	
		aac tct gtt act agc Asn Ser Val Thr Ser 1510	
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	Asn Glu Ile Glu	ggc acc cta aac aaa Gly Thr Leu Asn Lys 540	
		agg aaa gtg tot gac Arg Lys Val Ser Asp 1560	
		atc atg gac tat aac Ile Met Asp Tyr Asn 1575	

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tta cca tot ggo tgo tto aac acc ccg tcc att gaa aag ccc 5086 Leu Pro Ser Gly Cys Phe Asn Thr Pro Ser Ile Glu Lys Pro

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Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val

Ala Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr 65 70 75 80

Gly Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln 85 90 95

Pro His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln

Ala Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln

Tyr Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp 130 140

Ile Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe 145 155 160

Ala Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln 165 170 175

Tyr Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly

Phe Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu

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Leu 225	Glu	Gly	Arg	Pro	Ser 230	Ala	Tyr	Asn	Phe	Asp 235	Asn	Ser	Pro	Val	Leu 240
Gln	Glu	Trp	Val	Thr 245	Ala	Thr	Asp	Ile	Arg 250	Val	Thr	Leu	Asn	Arg 255	Leu
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Tyr	Tyr	Tyr 275	Ala	Ile	Ser	Asp	Phe 280	Ala	Val	Gly	Gly	Arg 285	Сув	Lys	Сув
Asn	Gly 290	His	Ala	Ser	Glu	Cys 295	Met	Lys	Asn	Glu	Phe 300	Asp	rys	Leu	Val
Cys 305	Asn	Суѕ	Lys	His	Asn 310	Thr	Tyr	Gly	Val	Asp 315	Cys	Glu	Lys	Ċys	Leu 320
Pro	Phe	Phe	Asn	Asp 325	Arg	Pro	Trp	Arg	Arg 330	Ala	Thr	Ala	Glu	Ser 335	Ala
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Asn 385	Phe	Phe	Arg	Leu	Gly 390	Asn	Asn	Glu	Ala	Cys 395	Ser	Ser	Cys	His	Cys 400
Ser	Pro	Val	Gly	Ser 405	Leu	Ser	Thr	Gln	Cys 410	Asp	Ser	туг	Gly	Arg 415	Сув
Ser	Cys	Lys	Pro 420	Gly	Val	Met	Gly	Asp 425	Lys	Cys	Asp	Arg	Cys 430	Gln	Pro
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Pro	Ser 450	Gly	Ser	Ile	Asp	Glu 455	Cys	Asn	Val	Glu	Thr 460	Gly	Arg	Сув	Val
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Tyr	Ser	Ile 515	Ser	Ser	Thr	Phe	Gln 520	Ile	Asp	Glu	Asp	Gly 525	Trp	Arg	Ala

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Asn Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu 835 840 845

Cys Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys 850 855 860

- Lys Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys 865 870 870 880
- Cys Lys Ala Cys Asn Cys Asn Pro Tyr Gly Thr Met Lys Gln Gln Ser 885 . 890 895
- Ser Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr 900 905 910
- Gly Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser 915 920 925
- Gly Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn 930 935 940
- Gly Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile 945 950 955 960
- Thr Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly
- Pro Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser
- Leu Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val 995 1000 1005
- Gly Asn Arg Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser 1010 1015 1020
- Trp Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp 025 1030 1035 1040
- Lys Val Ala Asp His Arg Val Lys Leu Gln Glu Leu Glu Ser Leu Ile 1045 1050 1055
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- Ala Glm Asp Val Lys Asp Val Asp Glm Asn Leu Met Asp Arg Leu Glm 1090 1095 1100
- Arg Val Asn Asn Thr Leu Ser Ser Gln Ile Ser Arg Leu Gln Asn Ile 105 1110 1115 1120
- Arg Asn Thr Ile Glu Glu Thr Gly Asn Leu Ala Glu Gln Ala Arg Ala 1125 1130 1135
- His Val Glu Asn Thr Glu Arg Leu Ile Glu Ile Ala Ser Arg Glu Leu 1140 1145 1150
- Glu Lys Ala Lys Val Ala Ala Ala Asn Val Ser Val Thr Gln Pro Glu 1155 1160 1165
- Ser Thr Gly Asp Pro Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg

1170 1175 1180

Lys Leu Ala Glu Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val 185 1190 1195 1200

- Ala Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu Leu 1205
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- Asn Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys 1235 1240 1245
- Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala 1250 1255 1260
- Val Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu 265 1270 1275 1280
- Thr Leu Glu Asn Glu Ala Asn Asn Ile Lys Met Glu Ala Glu Asn Leu 1285 1290 1295
- Glu Gln Leu Ile Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu 1300 1305 1310
- Asp Met Arg Gly Lys Glu Leu Glu Val Lys Asn Leu Leu Glu Lys Gly
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- Val Asn Asp Asn Lys Thr Ala Ala Glu Glu Ala Leu Arg Lys Ile Pro 1380 1385 1390
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- Lys Ala His Glu Ala Glu Arg Ile Ala Ser Ala Val Gln Lys Asn Ala 425  $1430 \hspace{1.5cm} 1440$
- Thr Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp 1445 1450 1455
- Leu Asp Asn Glu Val Asn Asn Met Leu Lys Gln Leu Gln Glu Ala Glu 1460 1465 1470
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- Ala Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala Arg 1490 1495 1500

Lys Ala Lys Asn Ser Val Thr Ser Leu Leu Ser Ile Ile Asn Asp Leu 1510 1515 Leu Glu Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn 1530 Glu Ile Glu Gly Thr Leu Asn Lys Ala Lys Asp Glu Met Lys Val Ser 1540 1545 Asp Leu Asp Arg Lys Val Ser Asp Leu Glu Asn Glu Ala Lys Lys Gln 1560 Glu Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile Glu Glu Ile Met Lys 1575 Asp Ile Arg Asn Leu Glu Asp Ile Arg Lys Thr Leu Pro Ser Gly Cys Phe Asn Thr Pro Ser Ile Glu Lys Pro <210> 23 <211> 4948 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)..(4728) <400> 23 cag gca gcc atg gac gag tgc acg gac gag ggc ggg cgg ccg cag cgc Gln Ala Ala Met Asp Glu Cys Thr Asp Glu Gly Gly Arg Pro Gln Arg 10 tgc atg ccc gag ttc gtc aac gcc gct ttc aac gtg act gtg gcc Cys Met Pro Glu Phe Val Asn Ala Phe Asn Val Thr Val Val Ala 20 25 acc aac acg tgt ggg act ccg ccc gag gaa tac tgt gtg cag acc ggg Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly 40 gtg acc ggg gtc acc aag too tgt cac ctg tgc gac gcc ggg cag ccc Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro cac ctg cag cac ggg gca gcc ttc ctg acc gac tac aac aac cag gcc His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala 70 gac acc acc tgg tgg caa agc cag acc atg ctg gcc ggg gtg cag tac Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr ccc age tee ate aac etc acg etg cac etg gga aaa get ttt gae ate Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile 100 105

acc Thr	tat Tyr	gtg Val 115	cgt Arg	ctc Leu	aag Lys	ttc Phe	cac His 120	acc Thr	agc Ser	cgc Arg	ccg Pro	gag Glu 125	agc Ser	ttt Phe	gcc Ala	384
				aca Thr												432
				tgc Cys												480
				999 999												528
				ccc Pro												576
				agc Ser												624
				gcc Ala												672
				gaa Glu												720
				tct Ser 245												768
				gag Glu												816
				aac Asn												864
				.cgg Arg												912
				tgt Cys												960
				tat Tyr 325												1008
				aca Thr												1056
ttc	ttc	cgc	ctt	ggc	aac	aat	gaa	gcc	tgc	tct	tca	tgc	cac	tgt	agt	1104

Phe	Phe	Arg 355	Leu	Gly	Asn	Asn	Glu 360	Ala	Сув	Ser	Ser	Cys 365	His	Cys	Ser	
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Ile Asn Gln Thr	atc act gaa Ile Thr Glu 1365	gcc aat gaa a Ala Asn Glu 1 1370	aag acc aga gaa gcc cag Lys Thr Arg Glu Ala Gln 1375	4128
	Ser Ala Ala		aca gag gcc aag aac aag Thr Glu Ala Lys Asn Lys 1390	4176
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1570 1575

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Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro  $50 \ \ 55 \ \ 60$ 

His Leu Cln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala 65 70 75 80

Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr  $85 \hspace{1cm} 90 \hspace{1cm} 95$ 

Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile 100 105 110

Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala 115 120 125

Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln Tyr 130 135 140

Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly Phe 145 150 155 160

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•	1000	#007S													PC.	
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Cys	Asp	Ala	Gly 95	Gln	Pro	His	Leu	Gln 100	His	Gly	Ala	Ala	Phe 105	Leu	Thr	
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				cag Gln												820
				ggc Gly												868
ttg Leu	tgt Cys 205	act Thr	gat Asp	gaa Glu	ttc Phe	agt Ser 210	gac Asp	att Ile	tct Ser	ccc Pro	ctc Leu 215	act Thr	ggg Gly	ggc Gly	aac Asn	916
gtg Val 220	gcc Ala	ttt Phe	tct Ser	acc Thr	ctg Leu 225	gaa Glu	gga Gly	agg Arg	ccc Pro	agc Ser 230	gcc Ala	tat Tyr	aac Asn	ttt Phe	gac Asp 235	964
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Val 220 aat Asn	agc Ser	Phe cct Pro	gtg Val	Thr ctg Leu	Leu 225 cag Gln	Glu gaa Glu act	tgg Trp	gta Val	act Thr 245	Ser 230 gcc Ala gaa	act Thr	gac Asp	atc Ile	aga Arg 250	Asp 235 gta Val	
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Val 220 aat Asn act Thr	agc Ser Ctt Leu 9tt Val	Phe cct Pro aat Asn ctc Leu 270	gtg Val cgc Arg 255 aag Lys	Thr ctg Leu 240 ctg Leu	Leu 225 cag Gln aac Asn tat Tyr	gaa Glu act Thr tat Tyr	tgg Trp ttt Phe tat Tyr 275	gta Val gga Gly 260 gcc Ala	act Thr 245 gat Asp atc Ile	Ser 230 gcc Ala gaa Glu tct Ser	act Thr gtg Val gat Asp	gac Asp ttt Phe ttt Phe 280	atc Ile aac Asn 265 gct Ala	aga Arg 250 gat Asp gta Val	Asp 235 gta Val ccc Pro ggt Gly	1012
Val 220 aat Asn act Thr aaa Lys ggc Gly	agc Ser ctt Leu gtt Val aga Arg 285 gat Asp	Phe cct Pro aat Asn ctc Leu 270 tgt Cys	gtg Val cgc Arg 255 aag Lys	tcc ctg Leu ctg Leu tcc Ser	cag Gln aac Asn tat Tyr	gaa Glu act Thr tat Tyr gga Gly 290 aat	tgg Trp ttt Phe tat Tyr 275 cac His	gta val gga Gly 260 gcc Ala gca Ala	Pro act Thr 245 gat Asp atc Ile agc Ser	gcc Ala gaa Glu tct Ser gag Glu aacc	act Thr gtg Val gat Asp tgt Cys 295 aca	Tyr gac Asp ttt Phe tttt phe 280 atgg Met tat	atc Ile aac Asn 265 gct Ala aag Lys	aga Arg 250 gat Asp gta Val aac Asn	Asp 235 gta Val ccc Pro ggt Gly gaa Glu	1012 1060 1108
val 220 aat Asn act Thr aaa Lys ggc Gly ttt Phe 300 tgt	agc Ser ctt Leu gtt Val aga Arg 285 gat Asp gaa	cct Pro aat Asn ctc Leu 270 tgts Cys aag Lys	gtg Val cgc Arg 255 aag Lys ctg Leu	tcc Ser tgtc Cys	Leu 225 cag Gln aac Asn tat Tyr aat Asn tgt Cys 305 cct	gaa Glu act Thr tat Tyr gga Gly 290 aat Asn	ttt Phe tat Tyr 275 cac His tgc Cys	gta Val gga Gly 260 gcc Ala gca Ala aaa Lys	Pro act Thr 245 gat Asp atc Ile agc Ser cat His	gcc Ala gaa Glu tct Ser gag Glu aacc Asn 310 cgg	act Thr gtgg Val gat Asp tgt Cys 295 aca Thr ccg	Tyr gac Asp ttt Phe ttt tpe 280 atg Met tat Tyr	atc Ile aac Asn 265 gct Ala aag Lys gga Gly	aga Arg 250 gat Asp gta Val aac Asn	Asp 235 gta Val ccc Pro ggt Gly gaa Glu gac Asp 315 gca Ala	1012 1060 1108

			335					340					345			
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gjå aaa	ggc Gly 365	cac His	tgt Cys	acc Thr	aac Asn	tgc Cys 370	cag Gln	gat Asp	aac Asn	aca Thr	gat Asp 375	ggc Gly	gcc Ala	cac His	tgt Cys	1396
gag Glu 380	agg Arg	tgc Cys	cga Arg	gag Glu	aac Asn 385	ttc Phe	ttc Phe	cgc Arg	ctt Leu	ggc Gly 390	aac Asn	aat Asn	gaa Glu	gcc Ala	tgc Cys 395	1444
tct Ser	tca Ser	tgc Cys	cac His	tgt Cys 400	agt Ser	cct Pro	gtg Val	ggc Gly	tct Ser 405	cta Leu	agc Ser	aca Thr	cag Gln	tgt Cys 410	gat Asp	1492
agt Ser	tac Tyr	ggc Gly	aga Arg 415	tgc Cys	agc Ser	tgt Cys	aag Lys	cca Pro 420	gga Gly	gtg Val	atg Met	ggg Gly	gac Asp 425	aaa Ļys	tgt Cys	1540
gac Asp	cgt Arg	tgc Cys 430	cag Gln	cct Pro	gga Gly	ttc Phe	cat His 435	tct Ser	ctc Leu	act Thr	gaa Glu	gca Ala 440	gga Gly	tgc Cys	agg Arg	1588
cca Pro	tgc Cys 445	tct Ser	tgt Cys	gat Asp	ccc Pro	tct Ser 450	ggc Gly	agc Ser	ata Ile	gat Asp	gaa Glu 455	tgt Cys	aat Asn	gtt Val	gaa Glu	1636
aca Thr 460	gga Gly	aga Arg	tgt Cys	gtt Val	tgc Cys 465	aaa Lys	gac Asp	aat Asn	gtc Val	gaa Glu 470	ggc	ttc Phe	aat Asn	tgt Cys	gaa Glu 475	1684
aga Arg	tgc Cys	aaa Lys	cct Pro	gga Gly 480	ttt Phe	ttt Phe	aat Asn	ctg Leu	gaa Glu 485	tca Ser	tct Ser	aat Asn	cct Pro	cgg Arg 490	ggt Gly	1732
tgc Cys	aca Thr	ccc Pro	tgc Cys 495	ttc Phe	tgc Cys	ttt Phe	999 Gly	cat His 500	tct Ser	tct Ser	gtc Val	tgt Cys	aca Thr 505	aac Asn	gct Ala	1780
gtt Val	ggc Gly	tac Tyr 510	agt Ser	gtt Val	tat Tyr	tct Ser	atc Ile 515	tcc Ser	tct Ser	acc Thr	ttt Phe	cag Gln 520	att Ile	gat Asp	gag Glu	1828
gat Asp	999 Gly 525	tgg Trp	cgt Arg	gcg Ala	gaa Glu	cag Gln 530	aga Arg	gat Asp	ggc Gly	tct Ser	gaa Glu 535	gca Ala	tct Ser	ctc Leu	gag Glu	1876
Trp 540	tcc Ser	Ser	Glu	Arg	Gln 545	Asp	Ile	Ala	Val	Ile 550	Ser	Asp	Ser	Tyr	Phe 555	1924
cct Pro	cgg Arg	tac Tyr	ttc Phe	att Ile 560	gct Ala	cct Pro	gca Ala	aag Lys	ttc Phe 565	ttg Leu	ggc Gly	aag Lys	cag Gln	gtg Val 570	ttg Leu	1972
agt Ser	tat Tyr	ggt Gly	cag Gln 575	aac Asn	ctc Leu	tcc Ser	ttc Phe	tcc Ser 580	ttt Phe	cga Arg	gtg Val	gac Asp	agg Arg 585	cga Arg	gat Asp	2020

act Thr	cgc Arg	ctc Leu 590	tct Ser	gcc Ala	gaa Glu	gac Asp	ctt Leu 595	gtg Val	ctt Leu	gag Glu	gga Gly	gct Ala 600	ggc Gly	tta Leu	aga Arg	2068
gta Val	tct Ser 605	gta Val	ccc Pro	ttg Leu	atc Ile	gct Ala 610	cag Gln	ggc	aat Asn	tcc Ser	tat Tyr 615	cca Pro	agt Ser	gag Glu	acc Thr	2116
				gtc Val												2164
				acc Thr 640												2212
				ata Ile												2260
				acc Thr												2308
				gag Glu												2356
				tgc Cys												2404
				cca Pro 720												2452
				gag Glu												2500
ggc Gly	ccg Pro	cac His 750	tgt Cys	gag Glu	aag Lys	tgc Cys	agt Ser 755	gat Asp	999 Gly	tac Tyr	tat Tyr	gga Gly 760	gat Asp	tca Ser	act Thr	2548
				tcc Ser												2596
				gtt Val												2644
				act Thr 800												2692
				ctg Leu												2740

tgc Cys	cag Gln	tgc Сув 830	agt Ser	gac Asp	aac Asn	atc Ile	gat Asp 635	ccc Pro	aac Asn	gca Ala	gtt Val	gga Gly 840	aat Asn	tgc Cys	aat Asn	2788
ege Arg	ttg Leu 845	acg Thr	gga Gly	gaa Glu	tgc Cys	ctg Leu 850	aag Lys	tgc Cys	atc Ile	tat Tyr	aac Asn 855	act Thr	gct Ala	ggc Gly	ttc Phe	2836
tat Tyr 860	tgt Cys	gac Asp	cgg Arg	tgc Cys	aaa Lys 865	gac Asp	gga Gly	ttt Phe	ttt Phe	gga Gly 870	aat Asn	ccc Pro	ctg Leu	gct Ala	ccc Pro 875	2884
aat Asn	cca Pro	gca Ala	gac Asp	aaa Lys 880	tgc Cys	aaa Lys	gcc Ala	tgc Cys	aat Asn 885	tgc Cys	aat Asn	ccg Pro	tat Tyr	890 890	acc Thr	2932
atg Met	aag Lys	cag Gln	cag Gln 895	agc Ser	agc Ser	tgt Cys	aac Asn	ccc Pro 900	gtg Val	acg Thr	Gly ggg	cag Gln	tgt Cys 905	gaa Glu	tgt Cys	2980
ttg Leu	cct Pro	cac His 910	gtg Val	act Thr	ggc Gly	cag Gln	gac Asp 915	tgt Cys	ggt Gly	gct Ala	tgt Cys	gac Asp 920	cct Pro	gga Gly	ttc Phe	3028
tac Tyr	aat Asn 925	ctg Leu	cag Gln	agt Ser	ggg Gly	caa Gln 930	ggc Gly	tgt Cys	gag Glu	agg Arg	tgt Cys 935	gac Asp	tgc Cys	cat His	gcc Ala	3076
			acc Thr													3124
tgc Cys	cag Gln	ccc Pro	ggc Gly	atc Ile 960	act Thr	ggt Gly	cag Gln	cac His	tgt Cys 965	gag Glu	cgc Arg	tgt Cys	gag Glu	gtc Val 970	aac Asn	3172
cac His	ttt Phe	999 Gly	ttt Phe 975	gga Gly	cct Pro	gaa Glu	ggc Gly	tgc Cys 980	aaa Lys	ccc Pro	tgt Cys	gac Asp	tgt Cys 985	cat His	cct Pro	3220
gag Glu	gga Gly	tct Ser 990	ctt Leu	tca Ser	ctt Leu	cag Gln	tgc Cys 995	aaa Lys	gat Asp	gat Asp	Gly	cgc Arg 000	tgt Cys	gaa Glu	tgc Cys	3268
Arg	gaa Glu .005	ggc Gly	ttt Phe	gtg Val	Gly	aat Asn 010	cgc Arg	tgt Cys	gac Asp	Gln	tgt Cys 015	gaa Glu	gaa Glu	aac Asn	tat Tyr	3316
ttc Phe 1020	Tyr	aat Asn	cgg Arg	Ser	tgg Trp 025	cct Pro	ggc Gly	tgc Cys	Gln	gaa Glu 030	tgt Cys	cca Pro	gct Ala	Cys	tac Tyr .035	3364
cgg Arg	ctg Leu	gta Val	aag Lys 1	gat Asp 040	aag Lys	gtt Val	gct Ala	Asp	cat His 045	aga Arg	gtg Val	aag Lys	Leu	cag Gln 050	gaa Glu	3412
tta Leu	gag Glu	Ser	ctc Leu 055	ata Ile	gca Ala	aac Asn	Leu	gga Gly 060	act Thr	g1 y 999	gat Asp	Glu	atg Met 065	gtg Val	aca Thr	3460
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Asp Gln Ala Phe Glu Asp Arg Leu Lys Glu Ala Glu Arg Glu Val Met 1070 1075 1080	
Asp Leu Leu Arg Glu Ala Gln Asp Val Lys Asp Val Asp Gln Asn Leu 1085 1090 1095	3556
atg gat cgc cta cag aga gtg aat aac act ctg tcc agc caa att agc Met Asp Arg Leu Gln Arg Val Asn Asn Thr Leu Ser Ser Gln Ile Ser 1100 1115	3604
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gaa caa gcg cgt gcc cat gta gag aac aca gag cgg ttg att gaa atc Glu Gln Ala Arg Ala His Val Glu Asn Thr Glu Arg Leu Ile Glu Ile 1135 1140 1145	3700
gca tcc aga gaa ctt gag aaa gca aaa gtc gct gct gcc aat gtg tca Ala Ser Arg Glu Leu Glu Lys Ala Lys Val Ala Ala Ala Asn Val Ser . 1150 1155 1160	3748
gtc act cag cca gaa tct aca ggg gac cca aac aac atg act ctt ttg Val Thr Gln Pro Glu Ser Thr Gly Asp Pro Asn Asn Met Thr Leu Leu 1165 1170 1175	3796
gca gaa gag gct cga aag ctt gct gaa cgt cat aaa cag gaa gct gat Ala Glu Glu Ala Arg Lys Leu Ala Glu Arg His Lys Gln Glu Ala Asp 1180 1185 1190 1195	3844
gac att gtt cga gtg gca aag aca gcc aat gat acg tca act gag gca Asp Ile Val Arg Val Ala Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala 1200 1205 1210	3892
tac aac ctg ctt ctg agg aca ctg gca gga gaa aat caa aca gca ttt Tyr Asn Leu Leu Leu Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe 1215 1220 1225	3940
Tyr Asn Leu Leu Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe	3940 3988
Tyr Asn Leu Leu Leu Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe 1215 1220 1225  gag att gaa gag ctt aat agg aag tat gaa caa gcg aag aac atc tca Glu Ile Glu Glu Leu Asn Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser	
Tyr Asn Leu Leu Leu Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe 1215  gag att gaa gag ctt aat agg aag tat gaa caa gcg aag aac atc tca Glu Ile Glu Glu Leu Asn Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser 1230  1235  1240  cag gat ctg gaa aaa caa gct gcc cga gta cat gag gag gcc aaa agg Gln Asp Leu Glu Lys Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg	3988
Tyr Asn Leu Leu Leu Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe 1215  gag att gaa gag ctt aat agg aag tat gaa caa gcg aag aac atc tca Glu Ile Glu Glu Leu Asn Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser 1230  1235  cag gat ctg gaa aaa caa gct gcc cga gta cat gag gag gcc aaa agg Gln Asp Leu Glu Lys Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg 1245  gcc ggt gac aaa gct gtg gag atc tat gcc agc gtg gct cag ctg agc Ala Gly Asp Lys Ala Val Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser	3988 4036
Tyr Asn Leu Leu Leu Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe 1215  gag att gaa gag ctt aat agg aag tat gaa caa gcg aag aac atc tca Glu Ile Glu Glu Leu Asn Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser 1230  1235  1240  cag gat ctg gaa aaa caa gct gcc cga gta cat gag gag gcc aaa agg Gln Asp Leu Glu Lys Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg 1245  1250  1255  gcc ggt gac aaa gct gtg gag atc tat gcc agc gtg gct cag ctg agc Ala Gly Asp Lys Ala Val Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser 1260  1265  1270  1275  cct ttg gac tct gag aca ctg gag aat gaa gca aat aac ata aag atg Pro Leu Asp Ser Glu Thr Leu Glu Asn Glu Ala Asn Asn Ile Lys Met	3988 4036 4084

1310	131	.5	1320
ctt ctg gag aa	a ggc aag act ga	a cag cag acc go	a gac caa ctc cta 427
Leu Leu Glu Ly	s Gly Lys Thr Gl	u Gln Gln Thr Al	a Asp Gln Leu Leu
1325	1330	133	5
gcc cga gct ga	t gct gcc aag gc	c ctc gct gaa ga	a gct gca aag aag 432
Ala Arg Ala As	p Ala Ala Lys Al	a Leu Ala Glu Gl	u Ala Ala Lys Lys
1340	1345	1350	1355
Gly Arg Asp Th	r Leu Gln Glu Al	a Asn Asp Ile Le 1365	c aac aac ctg aaa 437. u Asn Asn Leu Lys 1370
gat ttt gat ag	g Arg Val Asn As	t aac aag acg gc	c gca gag gag gca 442
Asp Phe Asp Ar		p Asn Lys Thr Al	a Ala Glu Glu Ala
137		1380	1385
cta agg aag at	t cct gcc atc aa	<b>n</b> Gln Thr Ile Th	t gaa gcc aat gaa 446
<b>Le</b> u Arg Lys Il	e Pro Ala Ile Ass		r Glu Ala Asn Glu
1390	139		1400
aag acc aga ga	a gcc cag cag gco	c ctg ggc agt gc	t gcg gcg gat gcc 4510
Lys Thr Arg Gl	u Ala Gln Gln Ala	a Leu Gly Ser Al	a Ala Ala Asp Ala
1405	1410	141	5
aca gag gcc aa	g aac aag gcc ca	t gag gcg gag ag	g atc gca agc gct 4564
Thr Glu Ala Ly	s Asn Lys Ala Hi	s Glu Ala Glu Ar	g Ile Ala Ser Ala
1420	1425	1430	1435
Val Gln Lys As	n Ala Thr Ser Thi 1440	r Lys Ala Glu Al 1445	t gaa aga act ttt 4612 a Glu Arg Thr Phe 1450
gca gaa gtt ac	r Asp Leu Asp Ası	t gag gtg aac aa	t atg ttg aag caa 4660
Ala Glu Val Th		n Glu Val Asn As	n Met Leu Lys Gln
145		1460	1465
ctg cag gaa gc	a gaa aaa gag cta	ı Lys Arg Lys Glı	a gat gac gct gac 4708
Leu Gln Glu Al	a Glu Lys Glu Let		n Asp Asp Ala Asp
1470	1475		1480
Gln Asp Met Me	t Met Ala Gly Met	t Ala Ser Gln Ala	
1485	1490	1499	
gag atc aat gc	c aga aaa gcc aaa	a aac tot gtt act	e agc ctc ctc agc 4804
Glu Ile Asn Ala	a Arg Lys Ala Lys	3 Asn Ser Val Th	r Ser Leu Leu Ser
1500	1505	1510	1515
att att aat gad Ile Ile Asn Asp	c ctc ttg gag cag p Leu Leu Glu Glr 1520	g ctg ggg cag ctg n Leu Gly Gln Leu 1525	g gat aca gtg gac 4852 1 Asp Thr Val Asp 1530
Leu Asn Lys Lei 153!	ı Asn Glu Ile Glu 5	o Gly Thr Leu Asr 1540	c aaa gcc aaa gat 4900 n Lys Ala Lys Asp 1545
gaa atg aag gto	e age gat ett gat	Arg Lys Val Ser	gac ctg gag aat 4948
Glu Met Lys Val	L Ser Asp Leu Asp		Asp Leu Glu Asn
1550	1555		1560

4996

5044

5092

5140

5330

gaa gcc aag aag cag gag gct gcc atc atg gac tat aac cga gat atc Glu Ala Lys Lys Gln Glu Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile 1565 1570 gag gag atc atg aag gac att cgc aat ctg gag gac atc agg aag acc Glu Glu Ile Met Lys Asp Ile Arg Asn Leu Glu Asp Ile Arg Lys Thr 1580 1585 tta cca tct ggc tgc ttc aac acc ccg tcc att gaa aag ccc gac tac Leu Pro Ser Gly Cys Phe Asn Thr Pro Ser Ile Glu Lys Pro Asp Tyr 1605 aag gac gac gat gac aag tagtgtettt agggetggaa ggeageatee Lys Asp Asp Asp Lys 1615 ctctgacagg ggggcagttg tgaggccaca gagtgccttg acacaaagat tacatttttc 5200 agacccccac tectetgetg etgtecatea etgteetttt gaaccaggaa aagteacaga 5260 gtttaaagag aagcaaatta aacateetga ategggaaca aagggtttta tetaataaag 5320 tqtctcttcc <210> 26 <211> 1617 <212> PRT <213> Homo sapiens Met Arg Gly Ser His Arg Ala Ala Pro Ala Leu Arg Pro Arg Gly Arg 1 5 10 15 Leu Trp Pro Val Leu Ala Val Leu Ala Ala Ala Ala Ala Ala Gly Cys \$20\$ \$25\$ 30Ala Gln Ala Ala Met Asp Glu Cys Thr Asp Glu Gly Gly Arg Pro Gln Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val Ala Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln 105 Ala Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp 135 Ile Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe

Ala Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln Tyr Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly Phe Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu Phe Ser Asp Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser Thr 215 Leu Glu Gly Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val Leu 225 230 235 240 Gln Glu Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg Leu Asn Thr Phe Gly Asp Glu Val Phe Asn Asp Pro Lys Val Leu Lys Ser 265 Tyr Tyr Tyr Ala Ile Ser Asp Phe Ala Val Gly Gly Arg Cys Lys Cys 275 280 285Asn Gly His Ala Ser Glu Cys Met Lys Asn Glu Phe Asp Lys Leu Val Cys Asn Cys Lys His Asn Thr Tyr Gly Val Asp Cys Glu Lys Cys Leu Pro Phe Phe Asn Asp Arg Pro Trp Arg Arg Ala Thr Ala Glu Ser Ala Ser Glu Cys Leu Pro Cys Asp Cys Asn Gly Arg Ser Gln Glu Cys Tyr Phe Asp Pro Glu Leu Tyr Arg Ser Thr Gly His Gly Gly His Cys Thr Asn Cys Gln Asp Asn Thr Asp Gly Ala His Cys Glu Arg Cys Arg Glu Asn Phe Phe Arg Leu Gly Asn Asn Glu Ala Cys Ser Ser Cys His Cys 385 390 395 400 Ser Cys Lys Pro Gly Val Met Gly Asp Lys Cys Asp Arg Cys Gln Pro 420 425 430Gly Phe His Ser Leu Thr Glu Ala Gly Cys Arg Pro Cys Ser Cys Asp 435 440 445 Pro Ser Gly Ser Ile Asp Glu Cys Asn Val Glu Thr Gly Arg Cys Val 455 Cys Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly 465 470 475 480

Phe Phe Asn Leu Glu Ser Ser Asn Pro Arg Gly Cys Thr Pro Cys Phe Cys Phe Gly His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val 500 510 Tyr Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Ala Glu Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg Gln Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile Ala Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn 565 570 575Leu Ser Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala 580 585 590Glu Asp Leu Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu 595 600 605 Ile Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Val 610  $\,$  620 Phe Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr 625 630 635 640 Pro Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile Arg Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr 665 Leu Ala Ser Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val Glu Ser Cys Thr Cys Pro Val Gly Tyr Gly Gln Gln Phe Cys Glu Met Cys 690 695 700 Leu Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu Gly Pro Tyr Ser Pro Cys Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu
725 730 735 Thr Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu 740 745 750Lys Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr Ala Gly Thr Ser Ser 755 760 765Asp Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val 770 780 Pro Lys Thr Lys Glu Val Val Cys Thr Asn Cys Pro Thr Gly Thr Thr

Gly Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu

805	810	815

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- Asn Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu 835 840 845
- Cys Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys 850 855 860
- Lys Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys 865 870 875 880
- Cys Lys Ala Cys Asn Cys Asn Pro Tyr Gly Thr Met Lys Gln Gln Ser 885 890 895
- Ser Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr 900 905 910
- Gly Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser 915 920 925
- Gly Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn 930 935 940
- Gly Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile 945 950 955 960.
- Thr Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly 965 970 975
- Pro Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser 980 985 990
- Leu Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val 995  $$1000\ \ \, 1005$
- Gly Asn Arg Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser 1010 1015 1020
- Trp Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp 025 1030 1035 1040
- Lys Val Ala Asp His Arg Val Lys Leu Gln Glu Leu Glu Ser Leu Ile 1045 1050 1055
- Ala Asn Leu Gly Thr Gly Asp Glu Met Val Thr Asp Gln Ala Phe Glu 1060 1065 1070
- Asp Arg Leu Lys Glu Ala Glu Arg Glu Val Met Asp Leu Leu Arg Glu 1075 1080 1085
- Ala Gln Asp Val Lys Asp Val Asp Gln Asn Leu Met Asp Arg Leu Gln 1090 1095 1100
- Arg Val Asn Asn Thr Leu Ser Ser Gln Ile Ser Arg Leu Gln Asn Ile 105 1110 1115 1120
- Arg Asn Thr Ile Glu Glu Thr Gly Asn Leu Ala Glu Gln Ala Arg Ala

His Val Glu Asn Thr Glu Arg Leu Ile Glu Ile Ala Ser Arg Glu Leu 1140 1145 1150

- Glu Lys Ala Lys Val Ala Ala Ala As<br/>n Val Ser Val Thr Gl<br/>n Pro Glu 1155 1160 1165
- Ser Thr Gly Asp Pro Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg 1170 1175 1180
- Lys Leu Ala Glu Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val 185 1190 1195 1200
- Ala Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu Leu 1205 1210 1215
- Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe Glu Ile Glu Glu Leu 1220 1225 1230
- Asn Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys 1235 1240 1245
- Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala 1250 1255 1260
- Val Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu 265 1270 1275 1280
- Thr Leu Glu Asn Glu Ala Asn Asn Ile Lys Met Glu Ala Glu Asn Leu 1285 1290 1295
- Glu Gln Leu Ile Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu 1300 1305 1310
- Asp Met Arg Gly Lys Glu Leu Glu Val Lys Asn Leu Leu Glu Lys Gly 1315 1320 . 1325
- Lys Thr Glu Gln Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala 1330 1335 1340
- Ala Lys Ala Leu Ala Glu Glu Ala Ala Lys Lys Gly Arg Asp Thr Leu 345 1350 1355 1360
- Gln Glu Ala Asn Asp Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg 1365 1370 1375
- Val Asn Asp Asn Lys Thr Ala Ala Glu Glu Ala Leu Arg Lys Ile Pro 1380 1385 1390
- Ala Ile Asn Gln Thr Ile Thr Glu Ala Asn Glu Lys Thr Arg Glu Ala 1395 1400 1405
- Gln Gln Ala Leu Gly Ser Ala Ala Asp Ala Thr Glu Ala Lys Asn 1410 1415 1420
- Lys Ala His Glu Ala Glu Arg Ile Ala Ser Ala Val Gln Lys Asn Ala 425 1430 1435 1440
- Thr Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp 1445 1450 1455

Leu Asp Asn Glu Val Asn Asn Met Leu Lys Gln Leu Gln Glu Ala Glu 1460 1465 1470

Lys Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Met 1475 1480 1485

Ala Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala Arg 1490 1495 1500

Lys Ala Lys Asn Ser Val Thr Ser Leu Leu Ser Ile Ile Asn Asp Leu 505 1510 1515 1520

Leu Glu Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn 1525 1530 1535

Glu Ile Glu Gly Thr Leu Asn Lys Ala Lys Asp Glu Met Lys Val Ser 1540 1545 1550

Asp Leu Asp Arg Lys Val Ser Asp Leu Glu Asn Glu Ala Lys Lys Gln 1555 1560 1565

Glu Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile Glu Glu Ile Met Lys 1570 1580

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Phe Asn Thr Pro Ser Ile Glu Lys Pro Asp Tyr Lys Asp Asp Asp Asp 1605 1610 1615

Lys

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acc aac acg tgt ggg act ccg ccc gag gaa tac tgt gtg cag acc ggg 144
Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly
35 40 45

gtg acc ggg gtc acc aag tcc tgt cac ctg tgc gac gcc ggg cag ccc 192

Val	Thr 50	Gly	Val	Thr	Lys	Ser 55	Сув	His	Leu	Сув	Asp 60	Ala	Gly	Gln	Pro	
cac His 65	ctg Leu	cag Gln	cac His	ggg Gly	gca Ala 70	gcc Ala	ttc Phe	ctg Leu	acc Thr	gac Asp 75	tac Tyr	aac Asn	aac Asn	cag Gln	gcc Ala 80	240
gac Asp	acc Thr	acc Thr	tgg Trp	tgg Trp 85	caa Gln	agc Ser	cag Gln	acc Thr	atg Met 90	ctg Leu	gcc Ala	999 Gly	gtg Val	cag Gln 95	tac Tyr	288
			atc Ile 100													336
			cgt Arg													384
			cgc Arg													432
			tcc Ser													480
atc Ile	agg Arg	aca Thr	gga Gly	999 Gly 165	gac Asp	gag Glu	cag Gln	cag Gln	gcc Ala 170	ttg Leu	tgt Cys	act Thr	gat Asp	gaa Glu 175	ttc Phe	528
			tct Ser 180													576
			ccc Pro													624
			act Thr													672
act Thr 225	ttt Phe	gga Gly	gat Asp	gaa Glu	gtg Val 230	ttt Phe	aac Asn	gat Asp	ccc Pro	aaa Lys 235	gtt Val	ctc Leu	aag Lys	tcc Ser	tat Tyr 240	720
			atc Ile													768
gga Gly	cac His	gca Ala	agc Ser 260	gag Glu	tgt Cys	atg Met	aag Lys	aac Asn 265	gaa Glu	ttt Phe	gat Asp	aag Lys	ctg Leu 270	gtg Val	tgt Cys	816
			cat His													864
			gac Asp													912

. .

	WO 0	0/667	30												PC1	Γ/US00/1
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gac Asp	cct Pro	gaa Glu	ctc Leu	tat Tyr 325	cgt Arg	tcc Ser	act Thr	ggc Gly	cat His 330	Gly	ggc Gly	cac His	tgt Cys	acc Thr 335	aac Asn	1008
tgc Cys	cag Gln	gat Asp	aac Asn 340	aca Thr	gat Asp	ggc	gcc Ala	cac His 345	tgt Cys	gag Glu	agg Arg	tgc Cys	cga Arg 350	gag Glu	aac Asn	1056
ttc Phe	ttc Phe	cgc Arg 355	ctt Leu	ggc	aac Asn	aat Asn	gaa Glu 360	gcc Ala	tgc Cys	tct Ser	tca Ser	tgc Cys 365	cac His	tgt Cys	agt Ser	1104
cct Pro	gtg Val 370	ggc Gly	tct Ser	cta Leu	agc Ser	aca Thr 375	cag Gln	tgt Cys	gat Asp	agt Ser	tac Tyr 380	ggc Gly	aga Arg	tgc Cys	agc Ser	1152
tgt Cys 385	aag Lys	cca Pro	gga Gly	gtg Val	atg Met 390	ggg ggg	gac Asp	aaa Lys	tgt Cya	gac Asp 395	cgt Arg	tgc Cys	cag Gln	cct Pro	gga Gly 400	1200
ttc Phe	cat His	tct Ser	ctc Leu	act Thr 405	gaa Glu	gca Ala	gga Gly	tgc Cys	agg Arg 410	cca Pro	tgc Cys	tct Ser	tgt Cys	gat Asp 415	ccc Pro	1248
tct Ser	ggc Gly	agc Ser	ata Ile 420	gat Asp	gaa Glu	tgt Cys	aat Asn	gtt Val 425	gaa Glu	aca Thr	gga Gly	aga Arg	tgt Cys 430	gtt Val	tgc Cys	1296
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ttt Phe 465	Gly 9 <b>9</b> 9	cat His	tct Ser	tct Ser	gtc Val 470	tgt Cys	aca Thr	aac Asn	gct Ala	gtt Val 475	ggc Gly	tac Tyr	agt Ser	gtt Val	tat Tyr 480	1440
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cag Gln	aga Arg	gat Asp	ggc Gly 500	tct Ser	gaa Glu	gca Ala	tct Ser	ctc Leu 505	gag Glu	tgg Trp	tcc Ser	tct Ser	gag Glu 510	agg Arg	caa Gln	1536
gat Asp	atc Ile	gcc Ala 515	gtg Val	atc Ile	tca Ser	gac Asp	agc Ser 520	tac Tyr	ttt Phe	cct Pro	cgg Arg	tac Tyr 525	ttc Phe	att Ile	gct Ala	1584

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													ccc Pro			1728
gct Ala	cag Gln	ggc Gly	aat Asn 580	tcc Ser	tat Tyr	cca Pro	agt Ser	gag Glu 585	acc Thr	act Thr	gtg Val	aag Lys	tat Tyr 590	gtc Val	ttc Phe	1776
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													gtc Val			1920
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													atg Met 670			2016
													agt Ser			2064
													cct Pro			2112
													tgt Cys			2160
													tcc Ser			2208
													gtt Val 750			2256
													acc Thr			2304
													ccc Pro			2352

aga Arg 785	aac Asn	ggc Gly	cct Pro	gtg Val	aga Arg 790	ctt Leu	tgc Cya	cgc Arg	ctg Leu	Сув	cag Gln	tgc Cys	agt Ser	gac Asp	Asn	2400
	gat	ccc	aac	qса		gga	aat	tgc	aat	795 cac	tta	acq	gga	оаа	800 tac	2448
Ile	Āsp	Pro	Asn	Ala 805	Val	Gly	Asn	Cys	Asn 810	Arg	Leu	Thr	Gly	Glu 815	Cys	2440
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								gaa Glu								2640
								gga Gly								2688
								cat His 905						Asn		2736
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ggt Gly	cag Gln 930	cac His	tgt Cys	gag Glu	cgc Arg	tgt Cys 935	gag Glu	gtc Val	aac Asn	cac His	ttt Phe 940	ggg Gly	ttt Phe	gga Gly	cct Pro	2832
								cat His								2880
								gaa Glu								2928
								aac Asn 985								2976
cct Pro	ggc Gly	tgc Cys 995	cag Gln	gaa Glu	tgt Cys	Pro	gct Ala 000	tgt Cys	tac Tyr	cgg Arg	Leu	gta Val	aag Lys	gat Asp	aag Lys	3024
Val					Val			cag Gln		Leu						3072
aac	ctt	gga	act	999	gat	gag	atg	gtg	aca	gat	caa	gcc	ttc	gag	gat	3120

Asn Leu Gly Thr Gly 1025	/ Asp Glu Met Val 1030	Thr Asp Gln Ala Phe	: Glu Asp 1040
aga cta aag gaa gc Arg Leu Lys Glu Al 104	a Glu Arg Glu Val	atg gac ctc ctt cgt Met Asp Leu Leu Arg 1050	gag gcc 3168 Glu Ala 1055
cag gat gtc aaa ga Gln Asp Val Lys As 1060	gtt gac cag aat Val Asp Gln Asn 1065	ttg atg gat cgc cta Leu Met Asp Arg Leu 1070	Gln Arg
gtg aat aac act ct Val Asn Asn Thr Le 1075	tcc agc caa att Ser Ser Gln Ile 1080	agc cgt tta cag aat Ser Arg Leu Gln Asn 1085	atc cgg 3264 Ile Arg
aat acc att gaa gag Asn Thr Ile Glu Glo 1090	g act gga aac ttg 1 Thr Gly Asn Leu 1095	gct gaa caa gcg cgt Ala Glu Gln Ala Arg 1100	gcc cat 3312 Ala His
gta gag aac aca gag Val Glu Asn Thr Glu 1105	g cgg ttg att gaa n Arg Leu Ile Glu 1110	atc gca tcc aga gaa Tle Ala Ser Arg Glu 1115	ctt gag 3360 Leu Glu 1120
	a Ala Ala Asn Val	tca gtc act cag cca Ser Val Thr Gln Pro 1130	
		ttg gca gaa gag gct Leu Ala Glu Glu Ala 1150	Arg Lys
		gat gac att gtt cga Asp Asp Ile Val Arg 1165	
aag aca gcc aat ga	aca tea act dad		
		gca tac aac ctg ctt Ala Tyr Asn Leu Leu 1180	
Lys Thr Ala Asn Ass 1170 aca ctg gca gga ga	o Thr Ser Thr Glu 1175 a aat caa aca gca	Ala Tyr Asn Leu Leu	Leu Arg
Lys Thr Ala Asn Asi 1170 aca ctg gca gga ga Thr Leu Ala Gly Gli 1185 agg aag tat gaa ca	o Thr Ser Thr Glu 1175 a aat caa aca gca 1 Asn Gln Thr Ala 1190 a gcg aag aac atc 1 Ala Lys Asn 1le	Ala Tyr Asn Leu Leu 1180 ttt gag att gaa gag Phe Glu Ile Glu Glu	t Leu Arg  Tott aat 3600 Leu Asn 1200 Laaa caa 3648
Lys Thr Ala Asn Asi 1170  aca ctg gca gga gai Thr Leu Ala Gly Gli 1185  agg aag tat gaa cai Arg Lys Tyr Glu Gli 1209 gct gcc cga gta cai	o Thr Ser Thr Glu 1175  a aat caa aca gca 1 Asn Gln Thr Ala 1190 a gcg aag aac atc 1 Ala Lys Asn Ile 5 c gag gag gcc aaa	Ala Tyr Asn Leu Leu 1180 ttt gag att gaa gag Phe Glu Ile Glu Glu 1195 tca cag gat ctg gaa Ser Gln Asp Leu Glu	t Leu Arg  1 ctt aat 3600 1 Leu Asn 1200 1 aaa caa 3648 1 Lys Gln 1215 1 gct gtg 3696 1 Ala Val
Lys Thr Ala Asn Asi 1170  aca ctg gca gga gai Thr Leu Ala Gly Gli 1185  agg aag tat gaa cai Arg Lys Tyr Glu Gli 1200  gct gcc cga gta cai Ala Ala Arg Val His 1220  gag atc tat gcc agg	o Thr Ser Thr Glu 1175  a aat caa aca gca 1 Asn Gln Thr Ala 1190  a gcg aag aac atc 1 Ala Lys Asn Ile 5 c gag gag gcc aaa 6 Glu Glu Ala Lys 1225 c gtg gct cag ctg	Ala Tyr Asn Leu Leu 1180  ttt gag att gaa gag Phe Glu Ile Glu Glu 1195  tca cag gat ctg gaa Ser Gln Asp Leu Glu 1210  agg gcc ggt gac aaa Arg Ala Gly Asp Lys	g ctt aat 3600 a Leu Asn 1200 a aaa caa 3648 a Lys Gln 1215 a gct gtg 3696 a Ala Val
Lys Thr Ala Asn Asi 1170  aca ctg gca gga gai Thr Leu Ala Gly Gli 1185  agg aag tat gaa cai Arg Lys Tyr Glu Gli 1200  gct gcc cga gta cai Ala Ala Arg Val His 1220  gag atc tat gcc agg Glu Ile Tyr Ala Sei 1235  ctg gag aat gaa gca	a aat caa aca gca a Asn Gln Thr Ala 1190 a gcg aag aac atc a Ala Lys Asn Ile c gag gag gcc aaa g Glu Glu Ala Lys 1225 c gtg gct cag ctg val Ala Gln Leu 1240 a aat aac ata aag	Ala Tyr Asn Leu Leu 1180  ttt gag att gaa gag Phe Glu Ile Glu Glu 1195  tca cag gat ctg gaa Ser Gln Asp Leu Glu 1210  agg gcc ggt gac aaa Arg Ala Gly Asp Lys 1230  agc cct ttg gac tct Ser Pro Leu Asp Ser	g ctt aat 3600 a Leu Asn 1200 a aaa caa 3648 a Lys Gln 1215 a gct gtg 3696 a Ala Val

1265	1270	1275	1280
Met Arg Gly Lys	gaa ctt gaa gto Glu Leu Glu Val 1285	c aag aac ctt ctg gag Lys Asn Leu Leu Glu 1290	g aaa ggc aag 3888 1 Lys Gly Lys 1295
act gaa cag cag Thr Glu Gln Gln 1300	Thr Ala Asp Glr	a ctc cta gcc cga gct 1 Leu Leu Ala Arg Ala 1305	c gat gct gcc 3936 A Asp Ala Ala 1310
aag gcc ctc gct Lys Ala Leu Ala 1315	gaa gaa gct gca Glu Glu Ala Ala 1320	a aag aag gga cgg gat a Lys Lys Gly Arg Asp ) 1325	Thr Leu Gln
gaa gct aat gac Glu Ala Asn Asp 1330	att ctc aac aac Ile Leu Asn Asr 1335	c Ctg aaa gat ttt gat n Leu Lys Asp Phe Asp 1340	t agg cgc gtg 4032 o Arg Arg Val
		g gag gca cta agg aag n Glu Ala Leu Arg Lys 1355	
Ile Asn Gln Thr	atc act gaa gco Ile Thr Glu Ala 1365	c aat gaa aag acc aga a Asn Glu Lys Thr Arg 1370	a gaa gcc cag 4128 g Glu Ala Gln 1375
	Ser Ala Ala Ala	g gat gcc aca gag gcc a Asp Ala Thr Glu Ala 1385	
gcc cat gag gcg Ala His Glu Ala 1395	gag agg atc gca Glu Arg Ile Ala 1400	a agc gct gtc caa aag a Ser Ala Val Gln Lys ) 1405	Asn Ala Thr
		a act ttt gca gaa gtt g Thr Phe Ala Glu Val 1420	
		g aag caa ctg cag gaa n Lys Gln Leu Gln Glu 1435	
Glu Leu Lys Arg		e get gac cag gac ato o Ala Asp Gln Asp Met 1450	
		gaa gee gag ate aat Glu Ala Glu Ile Asr 1465	
		ctc agc att att aat Leu Ser Ile Ile Asr 1485	Asp Leu Leu
gag cag ctg ggg Glu Gln Leu Gly 1490	cag ctg gat aca Gln Leu Asp Thr 1495	gtg gac ctg aat aag Val Asp Leu Asn Lys 1500	rcta aac gag 4512 Leu Asn Glu
		aaa gat gaa atg aag Lys Asp Glu Met Lys 1515	

4752

ctt gat agg aaa gtg tct gac ctg gag aat gaa gcc aag aag cag gag Leu Asp Arg Lys Val Ser Asp Leu Glu Asn Glu Ala Lys Lys Gln Glu 1525 1530 gct gcc atc atg gac tat aac cga gat atc gag gag atc atg aag gac Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile Glu Glu Ile Met Lys Asp 1540 1545 att cgc aat ctg gag gac atc agg aag acc tta cca tct ggc tgc ttc Ile Arg Asn Leu Glu Asp Ile Arg Lys Thr Leu Pro Ser Gly Cys Phe aac acc ccg tcc att gaa aag ccc gac tac aag gac gac gat gac aag Asn Thr Pro Ser Ile Glu Lys Pro Asp Tyr Lys Asp Asp Asp Asp Lys tagtgtettt agggetggaa ggeageatee etetgacagg ggggeagttg tgaggecaca 4812 gagtgccttg acacaaagat tacatttttc agacccccac tcctctgctg ctgtccatca 4872 ctgtcctttt gaaccaggaa aagtcacaga gtttaaagag aagcaaatta aacatcctga 4932 atcgggaaca aagggtttta tctaataaag tgtctcttcc <210> 28 <211> 1584 <212> PRT <213> Homo sapiens <400> 28 Gln Ala Ala Met Asp Glu Cys Thr Asp Glu Gly Gly Arg Pro Gln Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val Ala Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile 105 . Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala 120 Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln Tyr 135 Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly Phe 150 155

Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu Phe Ser Asp Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser Thr Leu Glu Gly Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val Leu Gln Glu Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg Leu Asn 215 Thr Phe Gly Asp Glu Val Phe Asn Asp Pro Lys Val Leu Lys Ser Tyr 225 230 235 240 Tyr Tyr Ala Ile Ser Asp Phe Ala Val Gly Gly Arg Cys Lys Cys Asn 245 250 255 Gly His Ala Ser Glu Cys Met Lys Asn Glu Phe Asp Lys Leu Val Cys 260 265 270 Asn Cys Lys His Asn Thr Tyr Gly Val Asp Cys Glu Lys Cys Leu Pro 275  $\phantom{0}280$   $\phantom{0}285$ Phe Phe Asn Asp Arg Pro Trp Arg Arg Ala Thr Ala Glu Ser Ala Ser 290 295 300 Glu Cys Leu Pro Cys Asp Cys Asn Gly Arg Ser Gln Glu Cys Tyr Phe 305 310 315 320 Asp Pro Glu Leu Tyr Arg Ser Thr Gly His Gly Gly His Cys Thr Asn 325 330 335 Cys Gln Asp Asn Thr Asp Gly Ala His Cys Glu Arg Cys Arg Glu Asn 345 Phe Phe Arg Leu Gly Asn Asn Glu Ala Cys Ser Ser Cys His Cys Ser 355 360 365 Pro Val Gly Ser Leu Ser Thr Gln Cys Asp Ser Tyr Gly Arg Cys Ser Cys Lys Pro Gly Val Met Gly Asp Lys Cys Asp Arg Cys Gln Pro Gly 385 390 395 400 Phe His Ser Leu Thr Glu Ala Gly Cys Arg Pro Cys Ser Cys Asp Pro 405 410 415Ser Gly Ser Ile Asp Glu Cys Asn Val Glu Thr Gly Arg Cys Val Cys Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly Phe 440 Phe Asn Leu Glu Ser Ser Asn Pro Arg Gly Cys Thr Pro Cys Phe Cys Phe Gly His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val Tyr

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Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Ala Glu Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg Gln 500 505 510Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile Ala 515 520 525 Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn Leu 535 Ser Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala Glu 550 Asp Leu Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu Ile Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Val Phe Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr Pro Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile Arg 610 620 Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr Leu 625 630 635 640 Ala Ser Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val Glu Ser Cys Thr Cys Pro Val Gly Tyr Gly Gly Gln Phe Cys Glu Met Cys Leu 660 665 670Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu Gly Pro Tyr Ser Pro Cys 675 680 685 Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu Thr 690 695 700 Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu Lys 705 710 715 720Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr Ala Gly Thr Ser Ser Asp 725 730 735 Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val Pro 740  $\phantom{000}745$   $\phantom{000}750$   $\phantom{0}00$ Lys Thr Lys Glu Val Val Cys Thr Asn Cys Pro Thr Gly Thr Thr Gly 755  $\phantom{000}760\phantom{000}$  760  $\phantom{0000}765\phantom{000}$ Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu Gly 770 785 Arg Asn Gly Pro Val Arg Leu Cys Arg Leu Cys Gln Cys Ser Asp Asn 785 790 795 800 Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu Cys

810 Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys Lys 825 Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys Cys Lys Ala Cys Asn Cys Asn Pro Tyr Gly Thr Met Lys Gln Gln Ser Ser Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr Gly Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser Gly 885 890 895 Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn Gly 900 905 910 Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile Thr Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly Pro 930 935 940 Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser Leu 945 950 955 960 Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val Gly 965 970 975 Asn Arg Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser Trp 985 Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp Lys 1000 Val Ala Asp His Arg Val Lys Leu Gln Glu Leu Glu Ser Leu Ile Ala Asn Leu Gly Thr Gly Asp Glu Met Val Thr Asp Gln Ala Phe Glu Asp Arg Leu Lys Glu Ala Glu Arg Glu Val Met Asp Leu Leu Arg Glu Ala 1050 Gln Asp Val Lys Asp Val Asp Gln Asn Leu Met Asp Arg Leu Gln Arg 1065 Val Asn Asn Thr Leu Ser Ser Gln Ile Ser Arg Leu Gln Asn Ile Arg 1080 Asn Thr Ile Glu Glu Thr Gly Asn Leu Ala Glu Gln Ala Arg Ala His

Val Glu Asn Thr Glu Arg Leu Ile Glu Ile Ala Ser Arg Glu Leu Glu

Lys Ala Lys Val Ala Ala Ala Asn Val Ser Val Thr Gln Pro Glu Ser

Thr Gly Asp Pro Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg Lys
1140 1145 1150

- Leu Ala Glu Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val Ala 1155 1160 1165
- Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu Leu Arg 1170 1175 1180
- Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe Glu Ile Glu Glu Leu Asn 1185 1190 1195 1200
- Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys Gln 1205 1210 1215
- Ala Ala Arg Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala Val 1220 1225 1230
- Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu Thr 1235 1240 1245
- Leu Glu Asn Glu Ala Asn Asn Ile Lys Met Glu Ala Glu Asn Leu Glu 1250 1255 1260
- Gln Leu Ile Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp 1265 1270 1275 1280
- Met Arg Gly Lys Glu Leu Glu Val Lys Asn Leu Leu Glu Lys Gly Lys 1285 1290 1295
- Thr Glu Gln Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala 1300 1305 1310
- Lys Ala Leu Ala Glu Glu Ala Ala Lys Lys Gly Arg Asp Thr Leu Gln 1315 1320 1325
- Glu Ala Asn Asp Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg Val 1330 1335 1340
- Asn Asp Asn Lys Thr Ala Ala Glu Glu Ala Leu Arg Lys Ile Pro Ala 1345 1350 1355 1360
- Ile Asn Gln Thr Ile Thr Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln 1365 1370 1375
- Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys 1380 1385 1390
- Ala His Glu Ala Glu Arg Ile Ala Ser Ala Val Gln Lys Asn Ala Thr 1395 1400 1405
- Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp Leu 1410 1415 1420
- Asp Asn Glu Val Asn Asn Met Leu Lys Gln Leu Gln Glu Ala Glu Lys 1425 1430 1435 1440
- Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Ala 1445 1450 1455

Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala Arg Lys 1460 1465 1470

- Ala Lys Asn Ser Val Thr Ser Leu Leu Ser Ile Ile Asn Asp Leu Leu 1475 1480 1485
- Glu Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu 1490 1495 1500
- Ile Glu Gly Thr Leu Asn Lys Ala Lys Asp Glu Met Lys Val Ser Asp 1505 1510 1515 1520
- Leu Asp Arg Lys Val Ser Asp Leu Glu Asn Glu Ala Lys Lys Gln Glu 1525 1530 1535
- Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile Glu Glu Ile Met Lys Asp 1540 1545 1550
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Thr Cys Pro Val Gly Tyr Gly Gly Gln Phe Cys Glu Thr Cys Leu Pro Gly Tyr Arg Arg Glu Thr Pro Ser Leu Gly Pro Tyr Ser Pro Cys Val 705 710 715 720 Leu Cys Thr Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu Thr Gly Val Cys Asp Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu Lys Cys 745 . Ser Asp Gly Tyr Tyr Gly Asp Ser Thr Leu Gly Thr Ser Ser Asp Cys 755  $\phantom{000}760$   $\phantom{000}765$ Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Ile Val Pro Lys 770 780 Thr Lys Glu Val Val Cys Thr His Cys Pro Thr Gly Thr Ala Gly Lys 785 790 795 800 Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu Gly Ser 805 810 815 Asn Gly Pro Val Arg Leu Cys Arg Pro Cys Gln Cys Asn Asp Asn Ile 820  $\phantom{\bigg|}$  825  $\phantom{\bigg|}$  830 Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu Cys Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys Lys Glu 855 Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys Cys Lys Ala Cys Ala Cys Asn Tyr Gly Thr Val Gln Gln Gln Ser Ser Cys Asn Pro Val Thr Gly Gln Cys Gln Cys Leu Pro His Val Ser Gly Arg Asp Cys Gly Thr Cys Asp Pro Gly Tyr Tyr Asn Leu Gln Ser Gly Gln Gly 915 920 925 Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn Gly Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile Thr Gly Gln 945 950 955 960 His Cys Glu Arg Cys Glu Thr Asn His Phe Gly Phe Gly Pro Glu Gly 965 970 975 Cys Lys Pro Cys Asp Cys His His Glu Gly Ser Leu Ser Leu Gln Cys 980 985 990 Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val Gly Asn Arg 995 1000 1005 Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser Trp Pro Gly

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- Lys Glu Ala Glu Arg Glu Val Thr Asp Leu Leu Arg Glu Ala Gln Glu 1075 1080 1085
- Val Lys Asp Val Asp Gln Asn Leu Met Asp Arg Leu Gln Arg Val Asn 1090 1095 1100
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- Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val Ala Lys Thr Ala 185 1190 1195 1200
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- Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala Val Glu Ile Tyr 1250 1255 1260
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- Glu Ala Asn Lys Ile Lys Lys Glu Ala Ala Asp Leu Asp Arg Leu Ile 1285 1290 1295
- Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp Met Arg Gly
  1300 1305 1310
- Lys Glu His Glu Val Lys Asn Leu Leu Glu Lys Gly Lys Ala Glu Gln 1315 1320 1325
- Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala Lys Ala Leu 1330 1335 1340

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- Gly Asn Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys Ala His Glu
- Ala Glu Arg Ile Ala Ser Ala Ala Gln Lys Asn Ala Thr Ser Thr Lys 1430 1435
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- Val Asn Gly Met Leu Arg Gln Leu Glu Glu Ala Glu Asn Glu Leu Lys 1465
- Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Ala Gly Met Ala 1480
- Ser Gln Ala Ala Gln Glu Ala Glu Leu Asn Ala Arg Lys Ala Lys Asn 1495 1500
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- Lys Val Ser Asp Leu Glu Ser Glu Ala Arg Lys Gln Glu Ala Ala Ile
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acg Thr	tgt Cys	<b>99</b> 9 Gly 35	Thr	ccg Pro	ccc Pro	gag Glu	gag Glu 40	tac Tyr	tgc Cys	gtg Val	cag Gln	act Thr 45	Gly 999	gtg Val	acc Thr	144
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caa Gln 65	cac His	G1A aaa	gca Ala	gcc Ala	ttc Phe 70	ctg Leu	acc Thr	gac Asp	tac Tyr	aac Asn 75	aac Asn	cag Gln	gcc Ala	gac Asp	acc Thr 80	240
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aat g Asn A 2																912
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gat a Asp A																1056
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tcc c Ser L																1248
agc a Ser T																1296
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	cc gac cag gac atg la Asp Gln Asp Met 45		

caa gcc gct cag gag gct gag ctc aat gcc aga aag gcc aaa aac tct Gln Ala Ala Gln Glu Ala Glu Leu Asn Ala Arg Lys Ala Lys Asn Ser 1460 gtc agc agc ctc ctc agc cag ctg aac aac ctc ttg gat cag cta gga Val Ser Ser Leu Leu Ser Gln Leu Asn Asn Leu Leu Asp Gln Leu Gly 1475 1485 cag ctg gac aca gtg gac ctg aac aag ctc aat gag atc gaa ggc tcc Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu Ile Glu Gly Ser 1500 ctg aac aaa gcc aaa gac gaa atg aag gcc agc gac ctg gac agg aag Leu Asn Lys Ala Lys Asp Glu Met Lys Ala Ser Asp Leu Asp Arg Lys 1510 1515 gtg tct gac ctg gag agc gag gct cgg aag cag gaa gca gcc atc atg Val Ser Asp Leu Glu Ser Glu Ala Arg Lys Gln Glu Ala Ala Ile Met 1525 1530 gac tat aac cgg gac ata gca gag atc att aag gat att cac aac ctg Asp Tyr Asn Arg Asp Ile Ala Glu Ile Ile Lys Asp Ile His Asn Leu 1545 gag gac atc aag aag acc cta cca acc ggc tgc ttc aac acc ccg tct 4704 Glu Asp Ile Lys Lys Thr Leu Pro Thr Gly Cys Phe Asn Thr Pro Ser 1560 atc gag aag ccc tagtggcgag agggctgtaa ggcagtgtcc ctgacagggg 4756 Ile Glu Lys Pro 1570 accetytgag gcctcggtgc cttgacacaa agattacact tttcagaccc ccacttctct 4816 gctgctctcc atcactgtcc ttttgaccca agaaaagtca gagtttaaag agaagcaagt 4876 taaacatett taaccaggaa caaagggttt tgeetaataa agteteteet eeaettetgt 4936 cagcacccta coggaacttt cocttgtttg cotgaagtca oggcatotto caggggcota 4996 eccacateat gtgaacettt taatgecagg geagacecag ecceeteece teteteaaca 5056 ccagcaggac ctatctcagt actcatgttt ctatgaagga aatctttggc tcctcatcgt 5116 agcattgaga tggccagtat gtccgctctg catcttctgc ctcctctttg aaaggaaata 5176 aacatecteg tgccaaaggt attggtcatt tagaatagtg gtggccatec atcagacatg 5236 ctggctggct gagcatagga cacagagcog tcgtgggtga gcgtagttac atgtgggtcc 5296 ccaggagaac atggctcaaa gatgcttagg gttcctcctg ttttcattga ctaggaagat 5356 gaatgtttcc caaatcctca ggcagctgat aaaaagtctg gatgggcagc tcgcacgcac 5416 cactacgtga ggtagctttt gatattttta taagcaggac ttaatgcaga agaaacagat 5476 gigataacca cicaagitti titccccaag tagtactaat tottaaagci tigitagigi 5536 tagtettgga actgttggta agatagetgt caaaacagtt gteetetaag gteatgacca 5596 atgaaagaag agcaaatctc cttttcccca tattttctgg gaagtggctg taatcgggat 5656

gtaaccgctc tcattaggat tccatgagtg catttctttt tctcttttc ttggagagag 5716 atgtgacgtt tggcccttag ctccattctc ttctgatgtt tccgttcttt ctagaactct 5776 tcagagcaca tcgttgtttg ccaggtcctg gtggcaaaca cccgctcaca gtgtttctca 5836 aggetgecaa ceccatetag tteetgeact ttgteggtee geccaeteca ageettteet 5896 ctgtgtggag agggaagatc catacgtggc atttcctagt gggcttctca acctctgatc 5956 ctcagctcgg tggtctcctt aagaccacac tgtgacagtt ccctgccaca catccccttc 6016 ctcctaccta cctgcctctg agattcatat ttagccttta acactatgca attttgtact 6076 ttgcgtacgg ggggaaagaa actattatct gacacactgg tgctattatt tgaaatttat 6136 attttttgtg tgaatggatt ttgtttatca tgattataga gtaaggaatt tatgtaaata 6196 tccccggtcc tcctagaacg gcactgtctg ctcacgtctc tgctcagttg tccctctcac 6256 tggcacagga acctgtacca tgcctggtca cgtcgtgcct ggtccccagt gttttgctcc 6316 acctctgcct tgtgtttgca gcaccttcac tgtctgaccg gaagcctgct cacctccaca 6376 acttgactga agagggccct cttccccgtg gctctgacca tctgagctgc agctcctcaa 6436 ggttctcatg cctgcccgga gcagtagcca agctgacagg gtaaagggat taggaacgtt 6496 tgtttgtgga accttcccac acgggtcagt tttctaaggg agcatgtgat gactgaacac 6556 ttgagggcat cagcaccgtg ctactgatga cagaggggag gctctgttca gcctgtctcc 6616 atcteggaga ttgccacaaa atcteagett ggcatcetee gaggeetttt gtgccaegge 6676 aagaaggegt ggcctcacca agttcagtgc tgattggcta gttcctctat tccgagctca 6736 ccaccttaac attttggtca cagttgcaag aaaatggctg aaacagacca ccaccagcat 6796 cctttgggtc aactccactc cagcaggccc gaggegctgg tgggtggggt gttttggttt 6856 gttttctcca gcttttgtgg tatattttta aacagaattt tattttttaa aatgaaagtt 6916 atttacaaga tgatacetta ttacgeteet tegacacage cattgettta ttgtatagtt 6976 ccaataatct gtattttatg taatgaaatg gacagaatgg ctgctgtaga atgcggggtg 7036 ccgcacagaa cagattgttt tatccctccc ccgcccccgc ccatggaatt ttcctttgat 7096 tccaactgtg gcccttttca atgtgccttc actttagctg tttgccttaa tctctacage 7156 cttccccct cagggagggc aataaagcgc aacacttggc attttttat gtttaaaaag 7216 7263 aaaacagtat tttatttata ataaaatctg aatatttgta acccttt

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<sup>&</sup>lt;210> 32

<sup>&</sup>lt;211> 1572

<sup>&</sup>lt;212> PRT

<sup>&</sup>lt;213> Mus musculus

	0 > 3														
Ala 1	Met	Asp	Glu	Cys 5	Ala	Asp	Glu	Gly	Gly 10	Arg	Pro	Gln	Arg	Суя 15	Met
Pro	Glu	Phe	Val 20	Asn	Ala	Ala	Phe	Asn 25		Thr	Val	Val	Ala 30	Thr	Asn
Thr	Сув	Gly 35	Thr	Pro	Pro	Glu	Glu 40	Tyr	Cys	Val	Gln	Thr 45	Gly	Val	Thr
Gly	Val 50	Thr	Lys	Ser	Сув	His 55	Leu	Cys	Asp	Ala	Gly 60	Gln	Gln	His	Leu
Gln 65	His	Gly	Ala	Ala	Phe 70	Leu	Thr	Asp	Tyr	Asn 75	Asn	Gln	Ala	Asp	Thr 80
Thr	Trp	Trp	Gln	Ser 85	Gln	Thr	Met	Leu	Ala 90	Gly	Val	Gln	Tyr	Pro 95	Asn
Ser	Ile	Asn	Leu 100	Thr	Leu	His	Leu	Gly 105	Lys	Ala	Phe	Asp	Ile 110	Thr	Tyr
Val	Arg	Leu 115	Lys	Phe	His	Thr	Ser 120	Arg	Pro	Glu	Ser	Phe 125	Ala	Ile	Tyr
Lys	Arg 130	Thr	Arg	Glu	Asp	Gly 135	Pro	Trp	Ile	Pro	Tyr 140	Gln	Tyr	Tyr	Ser
Gly 145	Ser	Cys	Glu	Asn	Thr 150	Tyr	Ser	Lys	Ala	Asn 155	Arg	Gly	Phe	Ile	Arg 160
Thr	Gly	Gly	Asp	Glu 165	Gln	Gln	Ala	Leu	Cys 170	Thr	Asp	Glu	Phe	Ser 175	Asp
Ile	Ser	Pro	Leu 180	Thr	Gly	Gly	Asn	Val 185	Ala	Phe	Ser	Thr	Leu 190	Ğlu	Gly
Arg	Pro	Ser 195	Ala	Ţyr	Asn	Phe	Asp 200	Asn	Ser	Pro	Val	Leu 205	Gln	Glu	Trp
Val	Thr 210	Ala	Thr	Asp	Ile	Arg 215	Val	Thr	Leu	Asn	Arg 220	Leu	Asn	Thr	Phe
Gly 225	Asp	Glu	Val	Phe	Asn 230	Asp	Pro	Lys	Val	Leu 235	Lys	Ser	Tyr	Tyr	Tyr 240
Ala	Ile	Ser	Asp	Phe 245	Ala	Val	Gly	Gly	Arg 250	Cys	Lys	Суз	Asn	Gly 255	His
Ala	Ser	Glu	Суз 260	Val	Lys	Asn	Glu	Phe 265	Asp	ГÀг	Leu	Met	Cys 270	Asn	Cys
Lys	His	Asn 275	Thr	Tyr	Gly	Val	Asp 280	Cys	Glu	Lys	Сув	Leu 285	Pro	Phe	Phe
Asn	Авр 290	Arg	Pro	Trp	Arg	Arg 295	Ala	Thr	Ala	Glu	Ser 300	Ala	Ser	Glu	Cys
Leu 305	Pro	Cys	Asp	Сув	Asn 310	Gly	Arg	Ser	Gln	Glu 315	Сув	Tyr	Phe	Asp	Pro 320

Glu Leu Tyr Arg Ser Thr Gly His Gly Gly His Cys Thr Asn Cys Arg 325 330 335 Asp Asn Thr Asp Gly Ala Lys Cys Glu Arg Cys Arg Glu Asn Phe Phe 340 350 Arg Leu Gly Asn Thr Glu Ala Cys Ser Pro Cys His Cys Ser Pro Val 355 360 365 Gly Ser Leu Ser Thr Gln Cys Asp Ser Tyr Gly Arg Cys Ser Cys Lys 370 380 Pro Gly Val Met Cly Asp Lys Cys Asp Arg Cys Gln Pro Gly Phe His 385 390 395 400 Ser Leu Thr Glu Ala Gly Cys Arg Pro Cys Ser Cys Asp Pro Ser Gly 405 410 415 Ser Thr Asp Glu Cys Asn Val Glu Thr Gly Arg Cys Val Cys Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly Phe Phe Asn 435 440 445 Leu Glu Ser Ser Asn Pro Lys Gly Cys Thr Pro Cys Phe Cys Phe Gly 450 455 His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val Tyr Asp Ile 465 470 475 480 Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Val Glu Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Asp Arg Gln Tyr Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile Ala Pro Val Lys Phe Leu Gly Asn Gln Val Leu Ser Tyr Gly Gln Asn Leu Ser Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala Glu Asp Leu Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu Ile Ala Gln 565 570 575 Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Ile Phe Arg Leu 580His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Ser Pro Phe Glu 595 600 605 Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile Arg Gly Thr 610 620 Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr Leu Gln Ser 625 635 640

Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val Glu Ser Cys Thr

	WU	W/00 /	30												P
				645					650					655	
Cys	Pro	Val	Gly 660	Tyr	Gly	Gly	Gln	Phe 665	Суя	Glu	Thr	Cys	Leu 670		Gly
Tyr	Arg	Arg 675	Glu	Thr	Pro	Ser	Leu 680	Gly	Pro	Tyr	Ser	Prc 685		Val	Leu
Сув	<b>T</b> hr 690	Cys	Asn	Gly	His	Ser 695	Glu	Thr	Cys	Asp	Pro 700	Glu	Thr	Gly	Va]
Cys 705	Asp	Cys	Arg	Asp	Asn 710	Thr	Ala	Gly	Pro	His 715	Сув	Glu	Lys	Сув	Ser 720
Asp	Gly	Tyr	Tyr	Gly 725	Asp	Ser	Thr	Leu	Gly 730	Thr	Ser	Ser	Asp	Сув 735	Glr
			Cys 740					745					750		
Lys	Glu	Val 755	Val	Cys	Thr	His	Cys 760	Pro	Thr	Gly	Thr	Ala 765	Gly	Lys	Arg
Cys	Glu 770	Leu	Cys	Asp	Asp	Gly 775	Tyr	Phe	Gly	Asp	Pro 780	Leu	Gly	Ser	Asn
Gly 785	Pro	Val	Arg	Leu	Cys 790	Arg	Pro	Сув	Gln	Cys 795	Asn	Asp	Asn	Ile	Asp 800
Pro	Asn	Ala	Val	Gly 805	Asn	Сув	Asn	Arg	Leu 810	Thr	Gly	Glu	Сув	Leu 815	Lys
Cys	Ile	Tyr	Asn 820	Thr	Ala	Gly	Phe	Tyr 825	Cys	Дар	Arg	Сув	Б В 3 О	Glu	Gly
Phe	Phe	Gly 835	Asn	Pro	Leu	Ala	Pro 840	Asn	Pro	Ala	Asp	Lys 845	Cya	Lys	Ala
Сув	Ala 850	Cys	Asn	Tyr	Gly	Thr 855	Val	Gln	Gln	Gln	Ser 860	Ser	Cys	Asn	Pro
Val 865	Thr	Gly	Gln	Сув	Gln 870	Сув	Leu	Pro	His	Val 875	Ser	Gly	Arg	Asp	Cys 880
Gly	Thr	Сув	Asp	Pro 885	Gly	Tyr	Tyr	Asn	Leu 890	Gln	Ser	Gly	Gln	Gly 895	Cys
Glu	Arg	Сув	Asp 900	Суз	His	Ala	Leu	Gly 905	Ser	Thr	Asn	Gly	Gln 910	Cys	Asp
Ile	Arg	Thr 915	Gly	Gln	Сув	Glu	Сув 920	Gln	Pro	Gly	Ile	Thr 925	Gly	Gln	His
Cys	Glu 930	Arg	аұЭ	Glu	Thr	Asn 935	His	Phe	Gly	Phe	Gly 940	Pro	Glu	Gly	Cys
Lув 945	Pro	Сув	Asp	Сув	His 950	His	Glu	Gly	Ser	Leu 955	Ser	Leu	Gln	Cys	Lys 960

Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val Gly Asn Arg Cys 965 970 975

Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser Trp Pro Gly Cys 980 985 990

- Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp Lys Ala Ala Glu 995 1000 1005
- His Arg Val Lys Leu Gln Glu Leu Glu Ser Leu Ile Ala Asn Leu Gly 1010 1015 1020
- Thr Gly Asp Asp Met Val Thr Asp Gln Ala Phe Glu Asp Arg Leu Lys 1025 1030 1035 1040
- Glu Ala Glu Arg Glu Val Thr Asp Leu Leu Arg Glu Ala Glu Glu Val 1045 1050 1055
- Lys Asp Val Asp Gln Asn Leu Met Asp Arg Leu Gln Arg Val Asn Ser 1060 1065 1070
- Ser Leu His Ser Gln Ile Ser Arg Leu Gln Asn Ile Arg Asn Thr Ile 1075 1080 1085
- Glu Glu Thr Gly Ile Leu Ala Glu Arg Ala Arg Ser Arg Val Glu Ser 1090 1095 1100
- Thr Glu Gln Leu Ile Glu Ile Ala Ser Arg Glu Leu Glu Lys Ala Lys 1105 1110 , 1115 1120
- Met Ala Ala Asn Val Ser Ile Thr Gln Pro Glu Ser Thr Gly Glu Pro 1125 1130 1135
- Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg Arg Leu Ala Glu Arg 1140 1145 1150
- His Lys Gln Glu Ala Asp Asp Ile Val Arg Val Ala Lys Thr Ala Asn 1155 1160 1165
- Glu Thr Ser Ala Glu Ala Tyr Asn Leu Leu Leu Arg Thr Leu Ala Gly 1170 1180
- Glu Asn Gln Thr Ala Leu Glu Ile Glu Glu Leu Asn Arg Lys Tyr Glu 1185 1190 1195 1200
- Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys Gln Ala Ala Arg Val 1205 1210 1215
- His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala Val Glu Ile Tyr Ala 1220 1225 1230  $\dot{}$
- Ser Val Ala Gln Leu Thr Pro Val Asp Ser Glu Ala Leu Glu Asn Glu 1235 1240 1245
- Ala Asn Lys Ile Lys Lys Glu Ala Ala Asp Leu Asp Arg Leu Ile Asp 1250 1255 1260
- Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp Met Arg Gly Lys 1265 1270 1275 1280
- Glu His Glu Val Lys Asn Leu Leu Glu Lys Gly Lys Ala Glu Gln Gln 1285 1290 1295

Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala Lys Ala Leu Ala 1300 1305 1310

- Glu Glu Ala Ala Lys Lys Gly Arg Ser Thr Leu Gln Glu Ala Asn Asp 1315 1320 1325
- Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg Val Asn Asp Asn Lys
  1330 1335
- Thr Ala Ala Glu Glu Ala Leu Arg Arg Ile Pro Ala Ile Asn Arg Thr 1345 1350 1355 1360
- Ile Ala Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln Leu Ala Leu Gly 1365 1370 1375
- Asn Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys Ala His Glu Ala 1380 1385 1390
- Glu Arg Ile Ala Ser Ala Ala Gln Lys Asn Ala Thr Ser Thr Lys Ala 1395 1400 1405
- Asp Ala Glu Arg Thr Phe Gly Glu Val Thr Asp Leu Asp Asn Glu Val 1410 1420 1420
- As nGly Met Leu Arg Gln Leu Glu Glu Ala Glu As nGlu Leu Lys Arg 1425 1430 1435 1440
- Lys Gln Asp Asp Ala Asp Gln Asp Met Met Ala Gly Met Ala Ser 1445 1450 1455
- Gln Ala Ala Gln Glu Ala Glu Leu Asn Ala Arg Lys Ala Lys Asn Ser 1460 1465 1470
- Val Ser Ser Leu Leu Ser Gln Leu Asn Asn Leu Leu Asp Gln Leu Gly 1475 1480 1485
- Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu Ile Glu Gly Ser 1490 1495 1500
- Leu Asn Lys Ala Lys Asp Glu Met Lys Ala Ser Asp Leu Asp Arg Lys 1505 1510 1515 1520
- Val Ser Asp Leu Glu Ser Glu Ala Arg Lys Gln Glu Ala Ala Ile Met 1525 1530 1535
- Asp Tyr Asn Arg Asp Ile Ala Glu Ile Ile Lys Asp Ile His Asn Leu 1540 1545 1550
- Glu Asp Ile Lys Lys Thr Leu Pro Thr Gly Cys Phe Asn Thr Pro Ser 1555 1560 1565

Ile Glu Lys Pro 1570